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JUNE 2004
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Nuclear Attacks in Orbit

Q&A with Bill Gates

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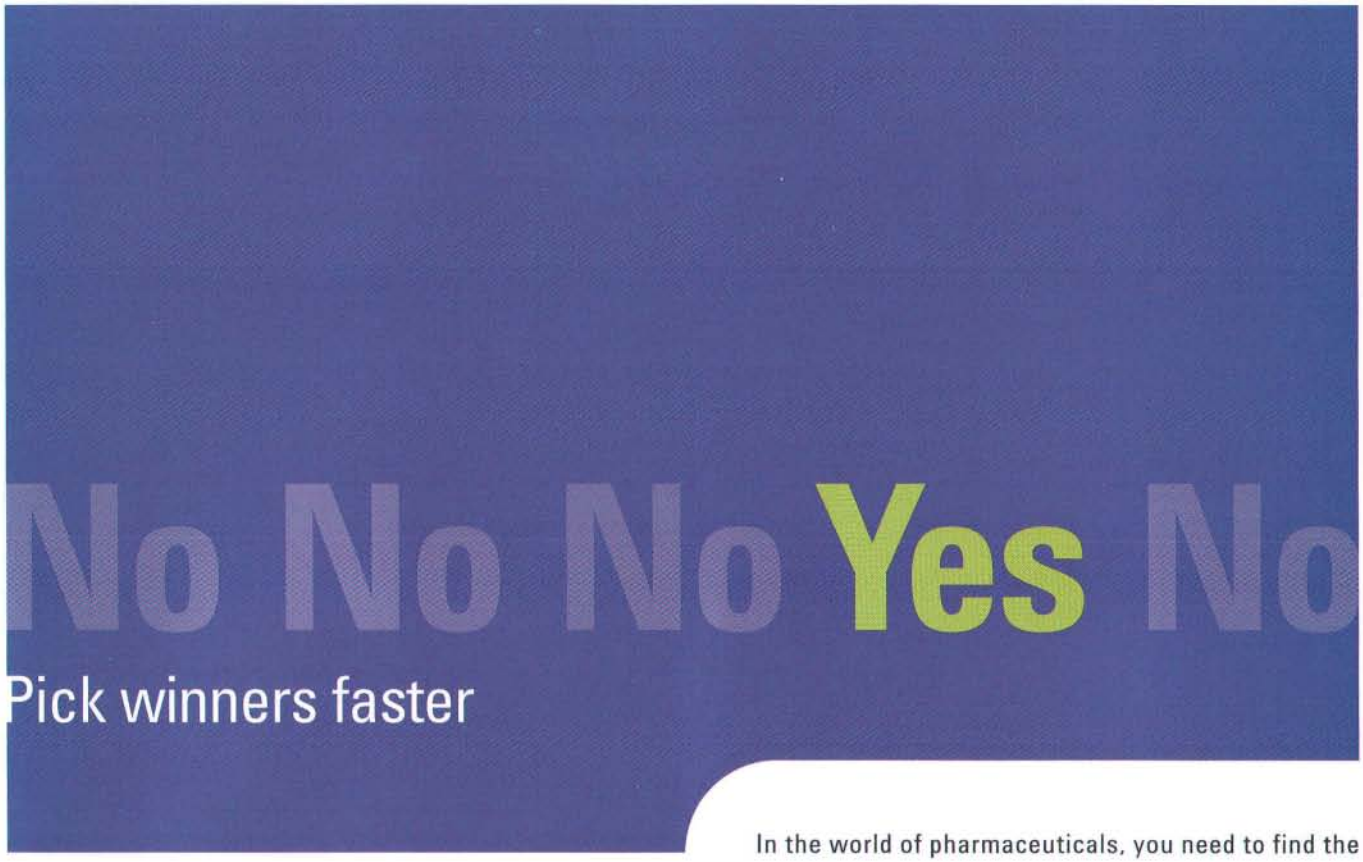

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june 2004

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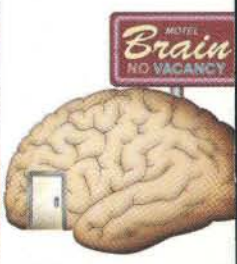

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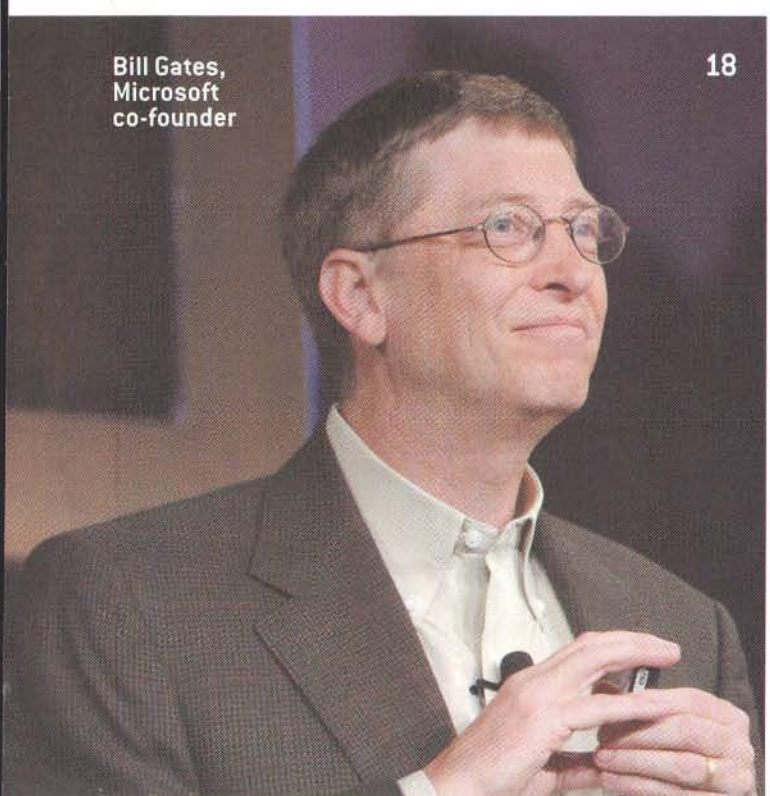

columns

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Stem Cells: A Way Forward

Korean investigators have extracted stem cells from a cloned human embryo. A Harvard biologist has developed 17 lines of human embryonic stem cells that he is making freely available to the scientific community. A ballot drive in California seeks to raise $3 billion for similar science [see "The Stem Cell Challenge," by Robert Lanza and Nadia Rosenthal, on page 60]. Unquestionably, research on human embryonic stem cells is moving forward.

STEM CELLS on ice.

KLAUS GULDBRANDSEN *Science Photo Library*

A conspicuously missing partner in that progress is the U.S. government. In August 2001 President George W. Bush allowed the use of federal funds for work on embryonic stem cells but only on those from sanctioned samples. Those cells lines, far fewer than were promised, have many limitations and may be unsuitable for future therapeutic applications.

As policy, the current rules are unsatisfying. The federal government simultaneously encourages stem cell research and treats it as odious. It has effectively ceded the tough moral decisions about work on embryos to private interests, states and other countries—although it might reverse course at any time. The federal funding restrictions present the illusion of compromise, but they are really a fig leaf for befuddlement.

Making a bad situation worse, policies on embryonic stem cells are bound up with the equally contentious debate over human cloning. The biomedical community has repudiated reproductive cloning—the creation of individuals who are genetic facsimiles. For some envisioned therapies, it might nonetheless be useful to briefly create an embryonic clone of an adult for the purpose of extracting stem cells. Investigators want this kind of therapeutic cloning to be legal. Many people, however, oppose human cloning in any form as unnatural. Because of legislative deadlock over therapeutic cloning, the U.S. has left itself without the reproductive cloning ban that everyone wants.

The stakes of dithering on these issues are high. If other countries jump ahead of the U.S. in stem cell therapeutics—and several have declared that intention—then both the biotechnology industry and patients will suffer. American companies might lose billions in revenue. Our government will have to decide whether to approve stem cell treatments developed overseas and also whether to allow Medicaid and Medicare to pay for them. Denying lifesaving treatments to the poor and elderly would be neither ethical nor politically popular. Yet approving the treatments would be morally inconsistent: the U.S. would be saying that it is wrong to conduct the research but fine to benefit from it.

If the administration has been looking for moral guidance out of this quandary, some can be found in "Reproduction and Responsibility," a report issued in March by the President's Council on Bioethics (available at www.bioethics.gov). Among other reforms, the council recommends that reproductive cloning be strictly banned, along with any other techniques for human procreation except by the fusion of human egg and sperm. It also urges that experiments on human embryos should be acceptable if the embryos are not maintained past a very early stage of development (no more than 14 days, for example). Those guidelines would neatly separate reproductive and therapeutic cloning while allowing investigators to collect the needed stem cells.

We hope that President Bush will take those recommendations to heart and support appropriate legislation to enact them. The government needs to commit to more meaningful policies on this research. The report's proposals are the best ones on the table.

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On the Web

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FEATURED THIS MONTH

Visit **www.sciam.com/ontheweb** to find these recent additions to the site:

Lab Rat Genome Sequenced

The rat has played a two-sided role in the history of human health. Infamous in the wild as a carrier of deadly illnesses such as the bubonic plague, the rat has also made its name in the laboratory as an indispensable model for studying human biology and disease as well as for developing and testing new drugs. Now it has become the third mammalian species (after humans and mice) to have its genome sequenced, promising greater insight into biomedicine, comparative biology and evolution.

Banished Thoughts Resurface in Dreams

"Wishes suppressed during the day assert themselves in dreams," wrote Sigmund Freud more than a century ago. New research suggests that not just wishes but all kinds of thoughts we bar from our minds while awake reappear when we sleep.

Devastating "Dust Bowl" Drought Explained

The eight-year drought that plagued the central U.S. in the 1930s, immortalized in John Steinbeck's *The Grapes of Wrath*, wracked the Great Plains with devastating dust storms and even extended into Mexico and Canada. Paramount to determining why the conditions were so severe and long-lasting is discerning what caused the drought in the first place. According to a recent study, unusual sea-surface temperatures could have been to blame.

Ask the Experts

What causes shin splints?
Claude T. Moorman III, director of sports medicine at Duke University Medical Center, explains.

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Letters

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AS THE OLD MAXIM goes, the proof that an article about a contentious subject is balanced is that both sides think it favored the other guy. Consider Richard Rosenfeld's "The Case of the Unsolved Crime Decline" [February]. Roy Jaruk, writing via e-mail, criticized the article's stance against laws that permit carrying concealed weapons for self-protection against criminals: Rosenfeld "claims that 'the case for "more guns, less crime" remains unproved.' Perhaps it does in the minds of ivory-tower liberals." A. C. Doyle of Boston chided the magazine, too: "Rosenfeld may back the NRA's push to allow concealed guns in schools and churches, but it is *not* based on any sort of rigorous research, nor should you try to conceal your own views against gun control under the guise of impartial reporting." A fair and balanced look at other February letters follows.

MORE THEORIES ABOUT CRIME

How sad! A professor of criminology building an argument on a mistaken assumption that there are national crime rates and national solutions ["The Case of the Unsolved Crime Decline," by Richard Rosenfeld]. Crime is not national—it, like politics, is local. New York City accounted for about 60 percent of the nation's homicide reduction in 1994 and 30 percent in 1995; similar effects occurred for robbery. Surely such numbers would skew any "national" trend.

The COMSTAT system that Rosenfeld mentions is based on a simple set of assumptions and directives. The formula resulted in crime declines 50 percent better than the national rates. In each of the cities that implemented COMSTAT—Baltimore; Newark, N.J.; New Orleans; and now Los Angeles—the system resulted in crime declines. The verdict is in, the case is solved: the answer is COMSTAT.

Louis R. Anemone
Chief of Department, N.Y.P.D. (retired)

Rosenfeld provides an unbalanced and inaccurate discussion of the literature. He puts forward the claim that 50 percent of the drop in murder arose from legalized abortion during the early 1970s (that study's authors now say that legalization explains even more of the decline). He fails to note that no studies confirm these findings, with others finding either no change or the opposite result.

When it comes to research that right-to-carry laws reduce violent crime, Rosenfeld writes: "Other scholars using similar data and methods, however, have not been able to reproduce Lott's results." But many academics have confirmed these findings, including Eric Helland (Claremont McKenna College), Alex Tabarrok (George Mason University), David Mustard (University of Georgia), Bruce Benson (Florida State University), John Whitley (University of Adelaide), David E. Olson (Loyola University Chicago), Florenz Plassmann (Binghamton University, New York), Nicolaus Tideman (Virginia Polytechnic Institute and State University), Carlisle Moody (College of William and Mary), Mark Cohen (Vanderbilt University), Stephen Bronars (University of Texas at Austin) and William Bartley (Vanderbilt).

John R. Lott, Jr.
American Enterprise Institute
Washington, D.C.

Rosenfeld deserves credit for mentioning the assertion that abortion has lowered the crime rate, but he is too dismissive of its veracity. We in the reproductive health care field have long known of this correlation. Our question is whether—now that legalized abortion has reached its lowest rate in 20 years—crime will again increase in a decade or two.

David Shobin, M.D., FACOG
Smithtown, N.Y.

The reason for the crime decline is clear:

Letters

prison populations grew by almost 70 percent in the decade. More prisoners mean fewer criminals on the streets.

We object to Rosenfeld's dismissal of John Lott's finding that concealed-weapon laws reduce violent crimes. Whereas some reports do not support Lott's results (including one by one of us, Marvell), at least as many corroborate the findings (including the other, Moody).

Finally, most of Rosenfeld's references are not peer-reviewed. A review of research on any topic would most likely come to the same conclusion—that is, a lack of consensus—if it relied on writings that did not pass peer review.

Thomas B. Marvell
Justec Research
Williamsburg, Va.
Carlisle Moody
Department of Economics
College of William and Mary

ROSENFELD REPLIES: *My article's central claim is that no single factor was responsible for the U.S. crime drop during the 1990s.*

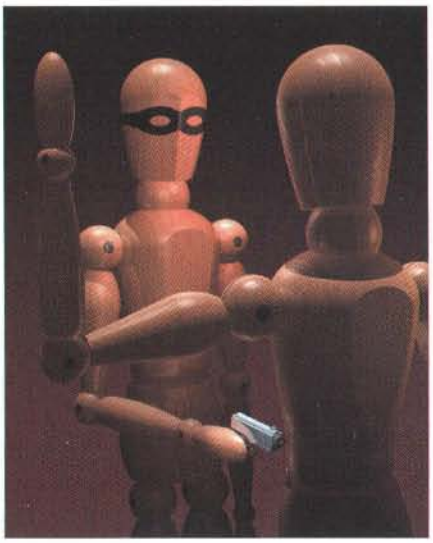
Contrary to Anemone, the 1990s crime drop was not limited to New York City and other jurisdictions that implemented COMSTAT. Violent crime also dropped sharply in other cities across the country, including Los Angeles, long before the arrival of COMSTAT.

I remain skeptical of Lott's claim that legislation permitting concealed firearms reduces crime. Lott lists researchers whose results match his own; he omits others, such as Ian Ayres and John Donohue, whose results offer no support. Reasonable modifications to Lott's models lead to contrary conclusions.

No one knows whether restrictions on abortion will, as Shobin argues, result in crime increases years from now. Even if they do, the challenge will be to isolate the effects from other conditions altering crime rates over time.

One factor that explains both the increase and decline in violent crime over the past two decades is the corresponding rise and fall in urban crack markets. Mass incarceration, as Marvell and Moody maintain, most likely had an effect on crime rates. But the incarceration rate has been escalating for 25 years, and violent crime rates declined for only roughly a decade.

Just as other factors contributed to the growth in violent crime during the 1980s, in spite of rising imprisonment, other factors contributed to the decline in violent crime during the 1990s, along with rising imprisonment. That appraisal, by the way, is much closer to a consensus view among analysts of crime trends, in and outside of peer-reviewed literature, than explanations that privilege incarceration or any other single factor.



SUPPLY AND DEMAND

Regarding SA Perspectives ["A Waste of Energy"], there is little doubt that the CAFE standard for SUVs should be amended. But your inference that such amendments would eliminate the need for 700 new power plants is absurd. Oil is generally not the fuel used to generate electricity. To further infer that the problem can be solved through conservation alone is without merit. This country desperately needs a comprehensive program that not only emphasizes conservation but deals with the real need to increase supply.

John Traina
CEO, Navitas Corporation

BEYOND THE UNIVERSE?

In "From Slowdown to Speedup," Adam G. Riess and Michael S. Turner report that explanations for inflation and dark energy are causing cosmologists heartburn. Maybe it's time to consider possibilities beyond our universe. Perhaps the universe's increasing rate of expansion is caused by the gravitational attraction of mass beyond the horizon. Or the nonuniform structure of our universe may reflect that of one from before the big bang.

Michael Meyers
Naperville, Ill.

RIESS AND TURNER REPLY: *Although we are certainly in need of creative ideas to understand the puzzle of cosmic acceleration, something beyond our horizon, essentially by definition, can have no influence on us. Even a spherical shell of matter just within the horizon would have no effect. According to a basic principle in gravitational physics, for a spherical distribution of matter, only the mass interior to your position contributes to gravity. Gravity simply cannot pull from the outside. The best that lumps distributed within the horizon could do is to accelerate our galaxy but not the whole universe, and the smoothness of the microwave background puts limits even on that.*

The line of investigation that is closest to Meyers's view is that cosmic acceleration arises from the local influence of additional spatial dimensions. As Georgi Dvali's "Out of the Darkness" [February] suggests, it is possible in string theory that other, invisible dimensions may by their very existence have a gravitational impact on us. Research into these possibilities is very active now.

ERRATA The "Cosmic Harmonics" diagram on page 36 in "The Cosmic Symphony," by Wayne Hu and Martin White, is mislabeled. The label "maximum compression" should be "maximum positive displacement" and "maximum rarefaction" should be "maximum negative displacement."

Steroids have three hexagonal rings and one pentagonal ring, not a central complex of four hexagonal carbon rings ["Doping by Design," by Steven Ashley, News Scan].

Smallpox is a DNA virus, not an RNA virus, and bubonic plague ceased to be a leading cause of death 250 years ago but remains a major cause of death to this day ["AIDS Resistance Thanks to Smallpox?" by Charles Choi, News Scan].

SLIM FILMS

50, 100 & 150 Years Ago
FROM SCIENTIFIC AMERICAN

Polio Gossip ▪ Wright Rumors ▪ Yak Yak Yak

JUNE 1954

VACCINE FEAR—"After several weeks of confusion about the safety of the new poliomyelitis vaccine, mass tests got under way last month. Walter Winchell had told his radio audience that the vaccine 'may be a killer' because one batch had been found with live virus. The National Foundation for Infantile Paralysis, which is conducting and financing the test, hastened to make clear that each batch of vaccine was subjected to a three-laboratory check. The foundation pointed out that Jonas Salk, who developed the vaccine, had given the commercial preparation to more than 4,000 Pittsburgh children, none of whom showed any untoward effects."

SILICON SOLAR CELL—"A little wafer of adulterated silicon which converts sunlight directly into electrical energy was unveiled last month by Bell Telephone Laboratories. This solar battery is an outgrowth of transistor research. It works at an efficiency of 6 per cent. Bell scientists believe that the figure can be raised to 10 per cent. The device is not likely to replace large-scale power plants—a 30,000 kilowatt battery would cover some 100 acres—but the company expects it to be useful as a small power source for such applications as rural telephone systems."

JUNE 1904

GRAND CANYON—"With the foresight and liberality that have characterized our government from the first, the Grand cañon of the Colorado River in Arizona will be placed under the care and custody of the government. Government surveyors have surveyed a section of the cañon, and the work will require almost a year to complete. To the geologist, the cañon offers an ever-increasing and endless field for study. To the sightseer and lover of the tremendous and fearful in nature, it is the most wondrous and gorgeous scenic field in the world."

AVIATION RESEARCH—"The flying machine invented by Orville and Wilbur Wright, which made a successful flight at Kitty Hawk, N.C., last December, had another trial near Dayton, Ohio, on May 26, which the brothers say was successful. Great secrecy was maintained about the test, and but few witnessed it. The machine after being propelled along a track for the distance of a hundred feet, rose in the air, and flew a short distance, when it dropped. This was due, the inventors say, to a derangement of the gasoline engine that furnishes the power. In the fall the propellers were broken, and the test could not be repeated."

BICYCLE CRAZE—acrobatics in Berlin, 1904

BICYCLE DARING—"In the field of loop-looping with the bicycle, which has become so immensely popular of late, wheelmen have developed an amount of zeal which is without doubt worthy of a better cause. The latest novelty is the invention of an ingenious wheelman of Berlin, Böttner by name, who has constructed a double loop [*see illustration*]. Just imagine with what velocity the performer is hurled through these two loops, and perhaps it may be possible to appreciate the stoical quietude of his nerves."

JUNE 1854

YAKS—"Geoffrey Saint-Hilaire, and other eminent naturalists in France, are beginning to consider the domestication of animals which have hitherto been known to Europe only as objects of scientific curiosity. They have recently received for the Jardin des Plantes a number of Yaks from China—an animal which Comte de Buffon (1707–1788) says 'is more precious than all the gold of the New World.' In Thibet and China this animal draws large loads, supplies milk, has flesh which is excellent, and hair which can be wrought into warm clothes. To naturalize him, therefore, in Europe, would be an immense service to mankind. By the way, the late Lord Derby made the attempt and failed."

FORESTRY

Diving for Dead Wood

SUBMARINE WITH A CHAIN SAW FOR ECO-FRIENDLY LOGGING BY SARAH SIMPSON

Tangled, ghostly limbs barely tickle the water's surface from below. Elaborate roots grip lakebeds, though perhaps not as strongly as they did the forest floor. Such is the fate of millions of acres of prime timber—flooded in the wake of hydroelectric dams, sacrificed to make electricity.

WATERLOGGED: Timber from a forest flooded under Lois Lake in British Columbia is lifted out of the water after being cut by Sawfish, a remotely operated vehicle seen in the background.

TRITON LOGGING

Most of these drowned trees were left for dead long ago. But in western Canada, some of them are experiencing a reincarnation of sorts. Chris Godsall, a sustainable forestry specialist based in Victoria, B.C., has cut more than 1,000 submerged trees since January, a feat made possible by his invention of the world's first logging submarine.

Decades of previous salvaging efforts—mainly for felled logs that sank in rivers and lakes on their way to a mill—demonstrated that even trees that have soaked for 100 or more years remain pristine. A lack of oxygen in the stagnant bottom waters where they lie protects them from rot. Once dried, the waterlogged wood can become flooring, paneling, furniture, ceiling beams—anything a fresh-cut tree would be good for.

Godsall estimates at least 200 million trees worth some $50 billion await harvest behind the more than 45,000 large dams worldwide. British Columbia alone could keep 30 logging subs busy full-time for at least 30 years, he says. But tapping this bounty has proved challenging.

Conventional efforts to cull underwater forests are inefficient or just plain dangerous. Sending divers with hydraulic chain saws—a common practice in Brazil and Malaysia—poses obvious health hazards; working from safer ground has serious limits. A typical North American operation, which might use

a crane anchored to a barge to pluck trees up by the roots and then lift them to the surface one by one, can go only about 60 feet deep. That puts 80 percent of the trees in an average lake out of reach, Godsall explains.

Eyeing the depths, Godsall founded Triton Logging—named for the man-fish of Greek mythology—in March 2000. Since then, he has enlisted the help of a dozen contractors to convert a factory-built ROV, or remotely operated vehicle, into Sawfish, a chain saw–wielding cutting machine that can dive at least 1,000 feet.

Working full-time since January at Lois Lake, an 8.5-mile-long, 450-foot-deep reservoir 120 miles north of Victoria, seasoned ROV pilot Craig Elder flies the Sawfish like a video-game junkie from a six-by-six-foot control room on a barge. The vehicle's eight video cameras and sonar device—connected to the control room by a thick cable—are Elder's eyes and ears as he navigates among labyrinthine branches of Douglas fir and cedar. "If you lose your concentration for three or four seconds, you're gone," he says. Untangling the tether from snarled branches using the ROV's awkward robotic claw can be excruciating.

When all goes well, Elder snuggles Sawfish up to a promising trunk, screws in and inflates a black air bag, and saws off the tree just below the screw. The tree shoots to the surface cut end up, hauled by what looks like a giant garbage bag. Elder can fell 36 trees on a single dive while workers on a tugboat remove the bags and hang the trees beneath a floating boom. The tug later tows the boom—trees dangling under it like crystals on a chandelier—to an unloading dock along the shore.

Although the heavy, saturated trees are 20 to 30 percent more expensive to haul to a mill than their dry counterparts, Triton keeps costs comparable to conventional logging by avoiding the expenses of building new roads, controlling pests and fire, and replanting trees, Godsall notes. "Everyone in the distribution of forest products believes there is going to be marketing potential for this," says Peter Keyes, a vice president for International Forest Products, the major U.S.-based wood exporter that has agreed to buy Triton's first harvest.

SAWFISH, operated by the Canadian firm Triton Logging, can dive at least 1,000 feet—as deep as any reservoir in the world.

Every waterlogged tree salvaged is one living tree saved, Godsall figures. That eco-friendly appeal may attract specialty buyers, which means Triton's logs could eventually demand a higher price, Keyes suggests, especially if they win the approval of Vermont-based SmartWood, the only organization that offers third-party certification for salvaged wood. For forests, an idea that's all wet promises to be a good thing.

TRITON LOGGING

WORLD HUNGER FOR WOOD

- **Nearly half the earth's indigenous forests have disappeared. Approximately 94 percent of all forest products consumed worldwide are harvested from the estimated 6.7 billion acres of original forest that remain; the rest is grown on plantations.**
- **An area of indigenous forest twice the size of New Jersey is cut every year to satisfy existing demand for wood products. Other threats—such as forest fires, illegal logging and clear-cutting for agriculture—wipe out another 64 acres every minute.**
- **Global demand for paper—the largest use of wood fiber—has increased fivefold since the 1950s and is expected to double again by 2050.**

SOURCES: Forest Certification Resource Center/Metafore (www.certifiedwood.org); Forest Enterprises (www.forestenterprises.co.nz)

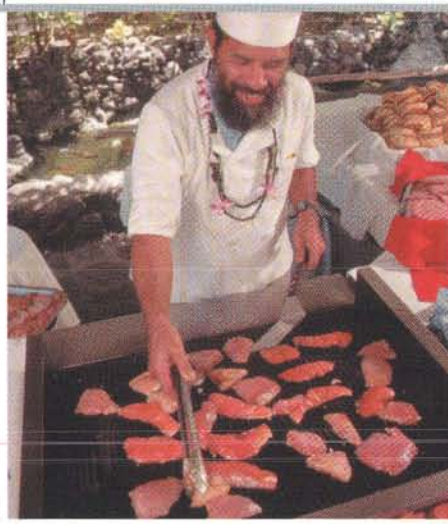
FOOD BIOLOGY

Homo carnivorous

ARE WE GENETICALLY OPTIMIZED TO DOWN CHICKEN WINGS? BY GARY STIX

The organization People for the Ethical Treatment of Animals entreats individuals to adopt vegetarianism as the "healthiest and most humane choice for animals, people and the planet." But don't stow away those carving knives just yet. Our carnivorous proclivities go back a long way—and our ability to cope with the drawbacks of meat eating (elevated cholesterol, parasites and infections) may derive from certain genes.

Meat eating, in fact, may have a lot to do with the *sapiens* tag that follows *Homo*. For



MEAT EATING provided an efficent way to obtain calories and nutrients for our ancestors. But modern life, absent the exertions required for the hunt, exceeds the ability of our genes to cope with the risks of meat consumption.

BOB KRIST *Corbis*

our ancestors, meat supplied a more concentrated package of calories and nutrients than weeds and berries. Not being the biggest and strongest members of the food chain, however, *Homo carnivorous* also required more cunning and wile to bring down that mastodon. One theory holds that a bigger brain and a longer period of nurturing and apprenticeship had to evolve to master the hunt. These changes also selected for extended life span, as prehistoric hunters were not thought to have achieved mastery of their skills until comparatively late in life.

But eating meat comes at a cost: increased risk of heart disease, stroke, cancer and diabetes. That must have been true back in the Pliocene, more than two million years ago, when meat was added to the menu of our plant-chomping forebears. University of Southern California gerontologist Caleb Finch and anthropologist Craig Stanford suggest in a paper in a recent *Quarterly Review of Biology* that there are at least eight "meat adaptive" genes that may have helped early humans cope with cholesterol, infections and other meat-derived ailments. "If they are correct, it may be possible to isolate some of the genes involved in the process and perhaps eventually determine when they evolved," says Hillard S. Kaplan, an anthropologist at the University of New Mexico who has worked with Finch.

One example is a variant of apolipoprotein E (the apoE3 allele), which mediates the uptake of cholesterol and fats by cells and plays a protective role in both cardiovascular and Alzheimer's disease. Other primates, such as chimpanzees, have a different apolipoprotein E gene and regularly experience elevated cholesterol in captivity, where they lead a sedentary existence and often have high-fat diets. In the wild, chimpanzees eat relatively little meat. "We humans have this obsession with cholesterol and saturated fat," Stanford notes. "In fact, as a species we're amazingly immune to its effects."

Stanford says that this research jibes with another recent finding that a genetic mutation that occurred 2.4 million years ago caused jaw sizes to diminish. Without the cumbersome chewing musculature, brains could grow bigger, marking the divergence of humans from apes. That period was when human ancestors may have first started using stone tools to butcher carcasses and so were less reliant on huge mandibles to process tough shells.

Finch and Stanford's paper is not an apologia for high-protein diets. "The problem with the Atkins diet is a failure to appreciate that in human prehistory there was no downside in beginning to eat a lot of meat, because meat was a rare and hard-to-get commodity," Stanford says, adding that eggs, another Atkins-friendly item, were available only in the spring, when wild birds nested. Daily bacon-and-eggs breakfasts are sure to foster untoward consequences without the levels of calorie expenditure of our ancestral hominid hunters and foragers. "Meat eating is a natural diet, given sufficient physical activity," Finch says.

Still, the relative scarcity of meat back then may go some way to help explain why no persuasion is needed to prompt the devouring of cheesesteaks and lamb chops, but getting the public to eat five or more servings of fruits and vegetables will remain an ever frustrating public health campaign.

FAST FACTS: MEAT GENES

Certain forms of eight genes may provide protection against disease risks associated with eating meat. Three are listed below:

- **ApoE3 is a common variant of the apolipoprotein E gene that transports cholesterol and reduces the risk of dementia.**
- **Prion genes influence how readily neurodegenerative prion proteins coded for by the genes are transmitted between species and influence the age of disease onset. The prion sickness mad cow disease affects only humans with a certain prion gene variation.**
- **Human lymphocyte antigens govern many aspects of immunity. The genes for these proteins have developed great diversity, probably to provide resistance to various pathogens carried by animal tissues.**

SPACE

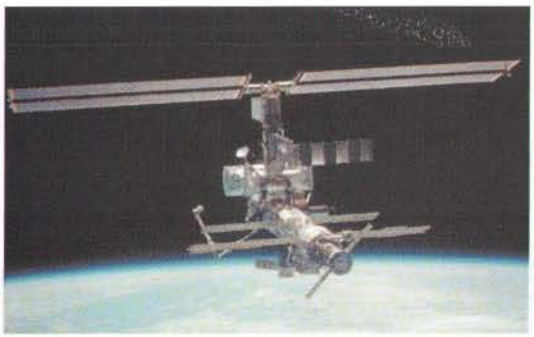
Eye on the Junk

SPACE STATION NOISES RENEW WORRY ABOUT ORBITAL DEBRIS **BY PHIL SCOTT**

Last November cosmonaut Alexander Kaleri was onboard the International Space Station (ISS) when he heard a loud bang. Kaleri didn't believe the sound was from balky equipment; rather it seemed to originate from outside. This past April the ISS crew reported hearing a similar clang. NASA has doubts whether the sounds really came from space junk hitting the station. But the noises have engineers paying renewed attention to the threat of orbital debris, which can act as missiles.

Space junk dates back to the beginning of the Space Age. The oldest known hunk is Vanguard 1, launched by the U.S. on March 17, 1958. Forty-six years later the number of

known orbital objects at least 10 centimeters wide has grown to nearly 11,000, and only several hundred of those are operational satellites, according to the U.S. Space Command in Cheyenne Mountain, Colo., which monitors these objects. Material in the lowest altitudes flies at around seven to eight kilometers a second. At that velocity, debris just a few millimeters wide would have the impact of a bowling ball moving at highway speeds.



MYSTERIOUS SOUNDS heard onboard the International Space Station made some people wonder if orbital debris hit the station. Ground stations track objects more than 10 centimeters wide, but smaller pieces can still do damage.

NASA

To take action against space junk, NASA engineers in 1996 explored the idea of using a ground-based laser to deflect it out of a spacecraft's path. The laser would ablate part of the junk's surface, creating a bit of thrust to move the piece out of the way. NASA even conceptualized mounting a laser on the ISS and firing away at debris like an old "Asteroids" video game. "But no one considered that seriously," explains Nicholas L. Johnson, head of the Orbital Debris Program Office at the Johnson Space Center in Houston. "It was projected to be a very big laser on the ground. Plus, [on the ISS] it would take a lot of energy to power—more than the space station could generate." The projects were also too costly for the level of perceived risk.

That left ISS engineers to design a passive system: shielding. "The ISS literally has hundreds of shields tailor-made," Johnson says. Each consists of an outer aluminum shielding with a "stuff shield" of bulletproof Nextel or Kevlar between the aluminum and the module. At 10 centimeters thick, the shielding will stop an object up to one centimeter in diameter moving at 10 kilometers a second.

The ISS can dodge the bigger chunks. Space Command identifies objects making possible close approaches to the station within 72 hours. If something is deemed a significant risk, Houston's Mission Control, in concert with its counterpart in Moscow, will alter the ISS's orbit by a couple kilometers, just enough to reduce the probability of collision. On average, mission controllers move the station once a year.

Last year Space Command added a higher-frequency radar unit to one of its ground antennas, enabling it to track objects between five and 10 centimeters. The single unit thus far has added 2,000 pieces to the total; Space Command's entire system is expected to be upgraded with the units within a few years. But tinier objects still pose a hazard: "Particles as small as a millimeter can do critical damage to the shuttle," Johnson notes, and they could be deadly to an astronaut on a spacewalk. As long as satellites go into orbit, it seems, junk will remain a threat.

Phil Scott writes about aviation and aerospace from New York City.

NEED TO KNOW: TRASHING SPACE

Currently several hundred operational satellites orbit the earth, each facing potential destruction by some four million kilograms of debris, most of it launched by the U.S.

- **Event that produced the most space junk:** explosion of a Pegasus rocket's upper stage in 1996, creating around 300,000 chunks bigger than four millimeters.
- **Largest hunk:** a Cosmos 382 Soviet lunar program test vehicle weighing 10 metric tons.
- **Most interesting debris:** Gemini astronaut Ed White's extra glove (no longer in orbit); a screwdriver and other tools lost by spacewalking shuttle astronauts.

NEURO-SCIENCE

Sitcoms on the Brain

DIFFERENT BRAIN AREAS "GET IT" AND FIND IT FUNNY BY MARINA KRAKOVSKY

What do you get when you cross a television comedy with a brain scanner? A team led by Joseph Moran and William Kelley at Dartmouth College's Center for Cognitive Neuroscience tried to find out. The researchers used functional magnetic resonance imaging (fMRI) on subjects watching episodes of either *Seinfeld* or *The Simpsons*. The resulting scans showed that "getting" a joke occurs in specific brain regions different from those involved in finding it funny.

This dissociation between the cognitive

and emotional parts of humor supports the scant previous research on humor's neural underpinnings, but the current study is the first to test the kind of humor people often experience in real life. "The idea of using sitcoms is very nice," comments Vinod Goel, a psychologist at York University in Toronto, noting that they are funnier than the puns and lawyer jokes he has used in his neuroimaging research.

JERRY, KRAMER AND GEORGE, from the TV series *Seinfeld*, helped to reveal that one part of the brain "gets" a joke and another part finds it funny.

An important feature of the Dartmouth study was that it neither asked the subjects to express what was funny nor tracked laughter or other overt physiological responses. Watching the shows in isolation, subjects weren't exactly busting a gut anyway, says Kelley—a good thing, because raucous laughter might have caused too much head movement for accurate fMRI readings. Asking subjects what was funny, Kelley believes, may have tainted the results of some earlier humor studies. After all, filling out a form or even just thinking about whether something is funny isn't the same as experiencing the pure joy of humor.

"The real trick is how, in the absence of laughter, do you assess humor?" Kelley says. The solution: rather than comparing individual responses with various points in the episodes, Kelley and his team simply assumed that the moments corresponding to the laugh track (or when an audience in a prior viewing laughed) were, on average, funnier than other parts of the episode. In analyzing the scans, they also assumed that humor detection comes just before humor appreciation.

The investigators found that instances of humor detection lit up the left inferior frontal and posterior temporal cortices—the left side of the brain. Humor appreciation, in contrast, led to spikes in activity in the emotional areas deeper inside—specifically, in the bilateral regions of the insular cortex and the amygdala.

Kelley believes that these results make sense. Past research has shown the left inferior frontal cortex to be involved in reconciling ambiguous meanings with prior knowledge. And ambiguity, incongruity and surprise are key elements in many jokes.

Kelley is the first to admit that his is just a preliminary study. Whereas the Dartmouth study assumed that humor detection comes just before humor appreciation, Goel points out that that sequence doesn't always hold true in his current research with single-panel comic strips. And although the laugh track seemed to be a reasonable rule of thumb in the Dartmouth work, that may be only because the subjects had been prescreened to like the cerebral, ironic style of the sitcoms they viewed.

"One of the biggest things that our study does is lead us to more questions," Kelley asserts. Future brain research could investigate whether these results extend to other types of humor, such as slapstick. But does the sitcom study at least help to explain why some people never seem to think a joke is funny, even when they clearly get it? "The individual-differences question is an interesting one," says Goel, but he argues that nonneurological explanations are more apt at this point. "If some people don't find *The Simpsons* funny, it's premature to say that they have a defective frontal lobe."

Marina Krakovsky, who often writes about the social sciences, can be reached at marina@stanfordalumni.org

NEED TO KNOW: PUN-ISHING HUMOR

"Doctor, how do I stop my nose from running?" "Stick your foot out and trip it up!" Unless you are younger than 10, you probably groaned. It is one thing to see the incongruity but quite another to have what humor researchers call the subjective experience of mirth. "Puns trigger that element of surprise or substitution, but they're not particularly funny to most adults," points out Steven Johnson, author of the book *Mind Wide Open: Your Brain and the Neuroscience of Everyday Life*. Many factors, including our age and life experience, determine what we find funny.

ENERGY

Power-Thrifty PCs

BILLION-DOLLAR SAVINGS WITH BETTER POWER SUPPLIES **BY STEVEN ASHLEY**

Putting a personal computer to sleep is typically the only means for users to conserve electricity, besides frequent, often inconvenient, shutdowns. Now a new focus of energy savings for the PC has emerged—its power supply.

When a PC is operating, its power supply typically converts only 60 to 70 percent of the 120-volt AC power into the 12-, 5- and 3.3-volt DC juice the internal system components need. The rest is mostly lost to heat. Each of the estimated 205 million PCs in the U.S. con-

sumes an average of about 300 kilowatt-hours of power annually, and that figure does not include the monitor's energy usage. Making PC power supplies 80 percent efficient, researchers say, could shave U.S. energy use by 1 to 2 percent and pare $1 billion or more from the nation's yearly electric bills while cutting emissions from generating plants significantly.

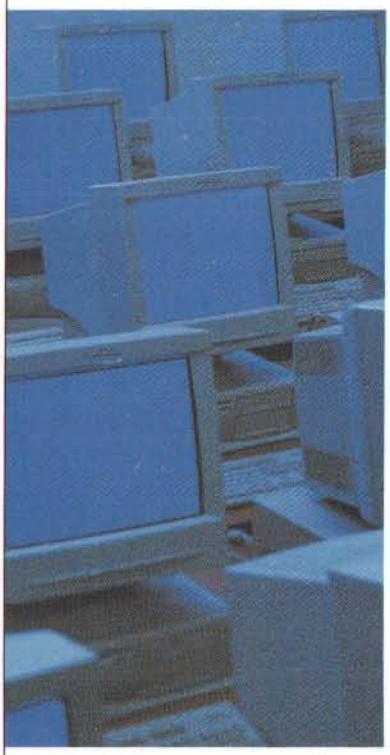
That is the goal of new energy-saving efforts being undertaken by federal and state agencies, environmental groups, electric utilities and the computer industry. "In the past," says Craig W. Hershberg, a product development manager in the U.S. Environmental Protection Agency's Energy Star program, "we promoted greater use of instantly available 'sleep modes' to save PC energy use, but we've found that approach to be less than totally satisfactory, because it relies on the users to implement," many of whom do not bother to do so. Moreover, often home computer and entertainment systems are networked and must stay on to be fully functional, which makes sleep-mode management difficult. Instead, Hershberg continues, "we're aiming at making the PC power supply more efficient—a target that doesn't require the user to do anything special."

Today's PCs use switching-mode power supplies (SMPS), says Michael Archer, chief technology officer at EOS, a division of Celetronix USA in Simi Valley, Calif. SMPS rely on a fast-acting switch to chop up the current, which is ultimately converted into low-voltage DC signals. Standard, "forced commutation" SMPS rely on a process "in which the current is made to turn on and off when it doesn't want to," Archer explains; in contrast, higher-efficiency "resonance-based" SMPS "only control the movement of that energy and so produce fewer losses." They can better match the demand for power with the supply and so produce less wasted energy.

In recent benchmark tests, the supplies that were 80 percent efficient cut energy use 15 to 25 percent across the board, reports Chris Calwell, director of policy and research for Ecos Consulting, a Portland, Ore.–based firm that promotes energy-efficient products. "Such improved units would cost about $5 more apiece wholesale but over four years of use would save about $25 in electricity costs." Ecos has formed partnerships with utilities to offer financial incentives to PC makers that install efficient power supplies.

Energy shavers are also targeting power-hungry central processing units (CPUs) and graphics cards. Intel and other chipmakers, for example, are now selling CPUs designed for laptops to desktop PC manufacturers. Laptop CPUs, designed to maximize battery life, can slow their processing speeds, thereby drawing less voltage. And engineers are looking for ways to improve the efficiency of the newest video cards, which may draw 50 to 60 watts each—as much as an entire computer.

Ecos and environmental watchdog Natural Resources Defense Council, working with Intel and others, have joined with the California Energy Commission and the EPA to launch a global competition to identify innovative design concepts that could boost efficiency (see www.efficientpowersupplies.org). Researchers at Ecos meanwhile are developing performance metrics by which PCs can be assessed in the same way that miles per gallon measures automotive fuel usage—with a benchmark score divided by the system's electrical consumption. This metric could serve as the basis for new PC energy efficiency ratings.



SLEEP MODE conserves energy, but better AC-to-DC conversion can save a lot more.

CORBIS

ENTOMOLOGY

The 17-Year Itch

BROOD X REAPPEARS, WITH CLUES TO CICADA BEHAVIOR **BY TABITHA M. POWLEDGE**

From late May through June, Brood X of the periodical cicadas will emerge from the ground, having spent the past 17 years as nymphs feeding off tree roots. After digging their way out and molting into adults, billions of the big, clumsy, red-eyed insects will sing their earsplitting love songs. Last seen in 1987, the brood will provide a prodigious if brief feast for birds, along with an incomparable opportunity for researchers.

BROOD X CICADAS last appeared in 1987. Every 17 years, this brood emerges from underground as nymphs, which soon molt (*left*) into adults that search for mates (*right*). In a few weeks, mating season ends and the adults die.

Fascinated naturalists have been writing about periodical cicadas for four centuries. But much remains unknown about the insects' periods or what triggers their synchronized appearances.

Brood X is perhaps the largest and best studied of the approximately 15 broods of periodical cicadas (researchers dispute the exact number). A brood emerges somewhere east of the Great Plains almost every spring. Worldwide, investigators have identified some 3,000 cicada species but know the life cycle for only a dozen or so. William Bradford, governor of the Plymouth Colony, first described periodical cicadas in 1633, although Native Americans probably knew of the creatures before then. The 17-year life cycle was firmly established less than a century later; by the mid-19th century, naturalists had recognized 13-year cicadas.

For more than 100 years, entranced mathematicians and biologists have tried to explain why periodical cicadas have evolved these prime-number cycles. One idea has been that the different cycles reduce competition for resources and interbreeding, because 13- and 17-year broods in the same locale will emerge together only once every 221 years. But in fact, different periodical cicada broods tend to be dispersed; little geographic overlap exists among most of them. And they do almost all their competitive eating during their long underground years, when they are sucking sap from tree roots.

Theorists have also argued that these oddball life cycles help cicadas to avoid predators and parasites with shorter, even-numbered life cycles. In 2001 researchers at the Max Planck Institute of Molecular Physiology in Dortmund, Germany, reported that prime-numbered life cycles emerged from their mathematical model of predator-prey relations.

Cicada researchers are deeply dubious about this explanation, however. The theory has not been falsified, notes evolutionary biologist Chris M. Simon of the University of Connecticut, because it cannot be tested. Her colleague David C. Marshall points out that true periodicity is rare in cicadas—separate groups of most species emerge every year. "If periodical cicadas evolved longer and longer life cycles to avoid a synchronizing parasitoid species," he notes, "then why has this apparently not happened in scores and scores of other cicada species that suffer predation and parasitism, not to mention in other kinds of insects and other animals?"

More curious to biologists such as Simon is the interaction among broods. As it does every spring, the University of Connecticut team will map cicada distributions, collect the insects for genetic analysis, and conduct small experiments on mating behavior. This year, Simon says, the researchers will scoop up samples from parts of Kentucky and Georgia where Brood X meets Broods XIX and XXIII of the 13-year cicadas and examine these specimens' DNA for evidence of past hybridization.

In addition, scientists are curious about developmental anomalies: broods sometimes drop or add a four-year stage called an instar. Entomologist Gene Kritsky of the College of Mount St. Joseph has reported accelerated development in Brood XIV, a 17-year cicada due out in 2008. He will be studying whether Brood XIV members come out this year, four years early, along with Brood X. In 2000 Kritsky also documented an early emergence of some of this year's Brood X cicadas. He hopes to be around to observe whether the eggs hatched in 2000 will stick to their new timetable and emerge in 2017—thus establishing a new brood—instead of reverting to the normal Brood X year, 2021.

Tabitha M. Powledge writes about biology and medicine from the greater Washington, D.C., area.

NOISY OPPORTUNITY

Investigating cicada life cycles is especially challenging because the insects are around for only a few weeks before dying and cannot be raised artificially. So researchers are glad to get e-mail and phone messages about emergences from amateur enthusiasts such as John Zyla in southern Maryland. Zyla, a military contractor, has turned himself into a respected cicada-brood mapper in the mid-Atlantic. "I don't have any special training," says Zyla, who works with the University of Connecticut cicada researchers. He has learned cicada songs, and such noisy creatures are easy to find. "People can make a big contribution," he declares, "by mapping [the insects'] distribution whenever the next brood comes out in their area. Chances are, no one else ever has."

University of Connecticut "Cicada Central":
http://collections2.eeb.uconn.edu/collections/cicadacentral/index.html

College of Mount St. Joseph cicada Web page:
www.msj.edu/cicada/

GREGORY HOOVER (*left*); GENE KRITSKY *College of Mount St. Joseph* (*right*)

Civic Culture

VARIABLE SENSE OF CIVIC DUTY AFFECTS VOTER TURNOUT **BY RODGER DOYLE**

Recent decades have seen a revival of interest in civic culture, sometimes called social capital or civic republicanism. As the term is generally used, it includes a high level of trust and tolerance, an egalitarian spirit, volunteerism, an interest in keeping informed, and participation in public affairs.

Political scientists Tom W. Rice of the University of Iowa and Jan L. Feldman of the University of Vermont have measured civic culture among ancestry groups in the U.S. They find that Americans of Scandinavian and British descent have the highest levels of civic culture, with those of French, Irish, German and Dutch descent having somewhat lower levels; those of Italian and Spanish descent have decidedly lower levels. (Spanish ancestry as measured in the study for the most part excludes Hispanic-Americans.) Furthermore, they conclude that these ethnic cultures are a continuation of the cultures in the country of origin. Thus, the 17th-century Puritan culture of England was transplanted to New England, and Minnesota saw the merging of 19th-century Swedish and German cultures.

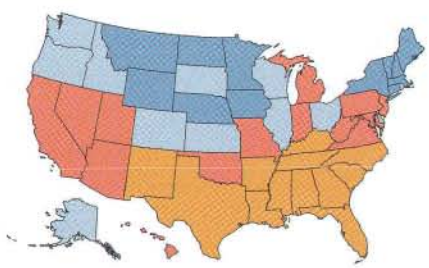
In separate work, Rice calculated indices of civic culture for each state based on a number of indicators, including crime rates, lawyers per capita, the default rate on student loans, the number of nonprofit organizations, civil-rights groups per capita, the proportion of state legislators who are women, and newspaper circulation per capita. Mapping these measures shows two distinct areas of strong civic culture: the West Central states (heavily populated by those of German and Scandinavian lineage) and New England–New York (where those of British lineage are numerous and have long wielded political influence). The low civic culture of the Southeast may reflect the mores of the particular British immigrants: the culture of the southern states originated to a substantial extent in the borderlands of northern England–southern Scotland and from Ulster, in contrast with the Puritan culture of New England, which originated in southern England. (Rice and Feldman could not split British ancestry into its components.)

Good civic culture would seem to go hand in hand with voting. Still, the coincidence is suggestive rather than conclusive. Other factors—such as education, which itself contributes to the ethos of civic culture—play an independent role in voter turnout.

Minnesota and Connecticut, whose people are among the best educated and most affluent in the nation, register high levels of civic culture. But the citizens of North Dakota and Montana, who have below-average education and income, are just as likely to vote, which may well reflect their Swedish and German roots. The high voting in Utah, which rates fairly low on the civic culture index, probably reflects high educational attainment plus high religiosity, which is positively related to voting.

Rodger Doyle can be reached at rdoyle2@adelphia.net

CIVIC CULTURE



Civic Culture Index, 1990

Bottom quartile | Second quartile | Third quartile | Top quartile

VOTER TURNOUT

Voter Turnout in Presidential Elections, 1980–2000

Bottom quartile | Second quartile | Third quartile | Top quartile

RODGER DOYLE

news SCAN

VOTING HIGHS AND LOWS

Average percent of citizens voting in presidential elections, 1980–2000:

States with lowest turnout:

Georgia: 53.6

Nevada: 54.5

South Carolina: 54.5

Tennessee: 55.7

West Virginia 56.0

States with highest turnout:

Minnesota: 74.3

Wisconsin: 72.4

North Dakota: 71.8

Maine: 71.4

Montana: 69.9

FURTHER READING

Civic Culture and Democracy from Europe to America. Tom W. Rice and Jan L. Feldman in *Journal of Politics*, Vol. 59, No. 4, pages 1143–1172; November 1997.

Civic Culture and Government Performance in the American States. Tom W. Rice and Alexander F. Sumberg in *Journal of Federalism*, Vol. 27, No. 1, pages 99–114; Winter 1997.

Civic Culture and Socioeconomic Development in the United States: A View from the States, 1880s–1990s. Tom W. Rice and Marshall Arnett in *Social Science Journal*, Vol. 38, No. 1, pages 39–51; Spring 2001.

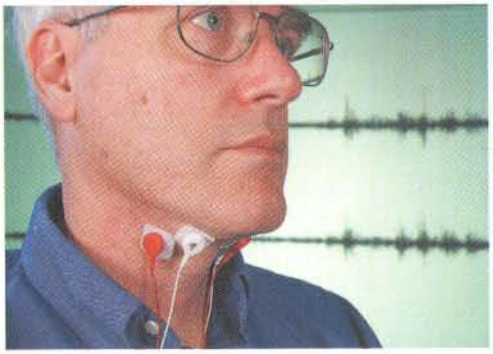
Current Population Reports: Voting and Registration in the Election of November 2000. Amie Jamieson, Hyon B. Shin and Jennifer Day. U.S. Census Bureau, February 2002.

SOURCES: Rice and Arnett, 2001 (civics map); U.S. Census Bureau (voting map)

LINGUISTICS

Read My Lips

If noise, injury or a thin atmosphere ever gets in the way of conversations between future astronauts, a NASA technology that recognizes unspoken words may come in handy. The tongue and vocal cords may not move when speaking silently, but they still receive speech signals. To pick up those signals, Chuck Jorgensen of the NASA Ames Research Center placed button-size sensors under the chin and on the neck of three subjects. A computer program recorded electrical activity whenever it rose above background noise and learned to associate the signals from an individual speaker with one of about 20 different words nearly 90 percent successfully, Jorgensen claims. By silently mouthing numbers, subjects browsed the Web without a keyboard. Hazmat crews, divers and the handicapped may benefit from subvocal speech recognition, says Jorgensen, whose findings were announced by NASA in March. *—JR Minkel*



UNSPOKEN TERMS: A computer program and sensors placed near the vocal cords and jaw can pick up silently mouthed words.

DOMINIC HART/NASA AMES RESEARCH CENTER

PSYCHOLOGY

Toddler Troubles

Preschool children who have difficulty sleeping may be more likely to drink alcohol and abuse other drugs later in life. University of Michigan at Ann Arbor researchers followed a group of 257 boys, between the ages of three and five, for 10 years. Boys who had habitual problems falling asleep or experienced fatigue during the day were about twice as likely as healthy sleepers to drink, smoke tobacco and use illicit drugs in their teens. The link remained even when the investigators controlled for other substance-abuse predictors, such as depression, attention deficits and parental alcoholism. Lack of sleep may cause a chemical imbalance, or sleep disorders and drug addiction may share a common brain pathway, says clinical psychologist Robert Zucker, senior author of the report, which appears in the April issue of *Alcoholism: Clinical and Experimental Research*. The risk isn't particularly huge, he notes, but improving early sleep habits could avoid future pitfalls. *—JR Minkel*

SLEEP PROBLEMS during childhood may presage alcohol and drug abuse.

JON FEINGERSH *Corbis*

BRIEF POINTS

- **The Brown Norway rat joins the human and mouse as the mammals to have had their genomes sequenced. The blueprint should help in biomedicine—human genes associated with disease have counterparts in the rat—and in evolution studies.**

  Nature, April 1, 2004; *Genome Research*, April 2004

- **Downsizing may sicken employees, but rapid workplace expansion also raises health risks and associated absenteeism, perhaps because of underlying recruitment and organization problems.**

  Lancet, April 10, 2004

ARCHAEOLOGY

The First Pet Cats

Ancient Egyptians may have had to shoo their cats away to read the morning papyrus, but historians have long suspected that the sphinx builders were not the first cat owners. A burial site in Cyprus now provides solid evidence that another civilization cleaned up after Felix's hairballs 5,000 years earlier. Researchers led by Jean-Denis Vigne of the CNRS–National Museum of Natural History in Paris found the complete skeleton of an eight-month-old cat lying 15 inches from the bones of a 30-year-old human. Both sets of remains were in the same sediment and at the same depth and showed the same degree of preservation, suggesting that feline and human were buried together about 9,500 years ago. Evidently, then, the domestication of cats occurred about 3,000 years after that of dogs and close to the time when farming began—when cats would have been useful in protecting stores of grain from mice. Pounce on the report in the April 9 *Science*. —*Philip Yam*

COMPANIONSHIP between cats and humans began much earlier than is popularly thought.

PHYSICS

Outer Quantum Limits

Cool an object, and thermal vibrations dictated by classical physics—Brownian motion—start quieting, eventually leaving only quantum jitters called zero-point energy. These particular quantum fluctuations, arising from the uncertainty principle, are routinely seen in photons and electrons, but not in bulkier objects. Keith Schwab of the National Security Agency and his colleagues at the University of Maryland have come achingly close to catching the transition between classical and quantum physics in a charged, vibrating sliver of gold and silicon nitride 0.01 millimeter long. The beam's vibrations pull electrons on or off a single electron transistor, whose resistance changes measurably as a result. Cooling the beam to 60 millikelvins brought the physicists to within a factor of 4 of the quantum limit. Calculations suggest that the beam would have to be cooled down to one millikelvin before zero-point fluctuations could be seen, but that may not be possible, Schwab says. Alternatively, a device for holding superconducting electrons may have to replace the single electron transistor. The cool details are in the April 2 *Science*. —*JR Minkel*

NEUROSCIENCE

Rewritable Appetite

Hardwired sensitivity to leptin, an appetite-suppressing hormone, seems to keep body weight hovering around a "set point." Evidence now indicates that leptin actually helps to write and rewrite the brain's circuitry in an appetite-regulating region of the hypothalamus called the arcuate nucleus. Researchers at the Rockefeller University and Yale University found that the brains of obese, leptin-deficient mice had more stimulatory connections than normal mice to neurons that promote feeding and weight gain and fewer connections to countervailing neurons. Giving the mice leptin restored the balance of connections even before the hormone reduced their appetite and weight; an appetite-stimulating hormone had the opposite effect. A second team from Oregon Health Sciences University discovered that arcuate nucleus cells have fewer branchings in leptin-deficient mice. Administering leptin just after birth mimicked a natural leptin surge and restored normal development, but giving leptin in adulthood had no effect on the number of branches, implying that leptin and nutrition during the first few weeks of life may have long-term effects on brain development. Both studies appear in the April 2 *Science*. —*JR Minkel*

WHETHER IT'S DURING CARNIVAL or Mardi Gras, a huge appetite may be a sign of neural rewiring.

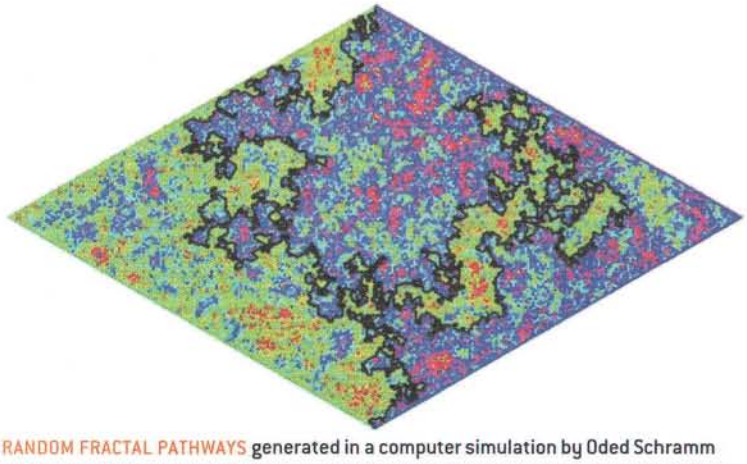
PHILIP YAM (*top*); BURSTEIN COLLECTION/CORBIS (*bottom*)

A Confederacy of Smarts

Can Microsoft's assemblage of all-star researchers transform computing? By GARY STIX

Thousands of Microsoft product developers—a sea of tieless shirts, dress pants and jeans—have descended on a nondescript building on the company's main campus in Redmond, Wash., one drizzly day in early March. Inside, rows of booths display the latest intellectual output from many of the 700 scientists who make up the software maker's research division. At one booth, there is a microphone that eliminates background noise. At another is software that converts a video image of a face into a graphic animation. Moving along, the visitor comes across a digital camera worn on the body of an exhibitor that snaps a frame every time the camera senses a change in temperature or light, creating a comprehensive record of a person's entire waking life. The annual event, called TechFest, is a means of ensuring that product developers stay aware of what the research side is doing.

The displays demonstrate a mix of ingenuity and cuteness typical of academic computer science departments. The Media Lab at the Massachusetts Institute of Technology immediately comes to mind. More startling than the displays themselves are some of the individuals walking the floor at the exhibition. Among them are engineers, mathematicians and programmers, some of whose ponytails are now graying, who would be shoo-ins for a Computer Science Hall of Fame. Meet C. Gordon Bell, an inventor of the minicomputer. Or James Kajiya, creator of some of the key mathematics underlying computer graphics rendering and winner of an Academy Award for technical achievement. Then there is James Gray, a giant in databases. These legendary figures have not come for a casual visit. During the past 13 years, using its enormous cash stockpiles, Microsoft has hired scores of these techno-wizards from universities and competitors to create one of the largest concentrations of talent the field has ever seen.



RANDOM FRACTAL PATHWAYS generated in a computer simulation by Oded Schramm and Scott Sheffield of the theory group at Microsoft Research reveal a type of pattern that may be useful in the modeling of quantum field theory or the contours of a crystal surface. This basic research bears no direct relation to any Microsoft product.

Microsoft started its own research laboratory in 1991, at a time when many of the bellwethers of corporate innovation, including IBM Research and AT&T Bell Laboratories, were trying to realign their missions to make themselves a lot more like advanced development groups. The ensuing upheavals caused more than a few researchers there to head for the door. Microsoft took the opposite route. Nathan Myhrvold, then the company's vice president of advanced technology and business development, had been militating for several years for a research laboratory, an oddity for a software developer. His case was undermined somewhat by the persistent inability of Xerox's Palo Alto Research Center (PARC) to capitalize on computer science innovations such as the graphical user interface, technologies close to Microsoft's area of business.

The lesson from the Xerox PARC experience that had turned into industry-wide prevailing wisdom was that pure research was simply a losing proposition. At the time, "I felt that was stupid, and, on the flip side, it was an opportunity," recalls Myhrvold, who left Microsoft four years ago to form a firm to create inventions. In the early 1990s the theoretical physicist turned corporate executive viewed the prospect as a cold, calcu-

MICROSOFT RESEARCH

lated wager: "If you say that Microsoft is a company that is going to spend money now for things that won't happen for five years and we'll hire really smart people and we'll work in really important areas and, if those areas succeed, we're going to make a pile of money on it, I think that you can't help but win that bet."

Famous for his technophilic proclivities, Microsoft founder Bill Gates gave Myhrvold the go-ahead to start roaming the country to lure the best and the brightest to greater Seattle. The early days were spent in planning how to avoid PARC's mistakes. At first, Microsoft Research confined its operations to Redmond, close to product developers, a decision not to repeat the ill-fated PARC experience. "The distance between Palo Alto and Rochester [the location of Xerox's headquarters] was enormous," says Gordon Bell, who advised Myhrvold during the start-up phase. "There was a huge cultural gap as well as a physical gap."

Finding a few smart people required an intensive sales job. "It was very tough hiring people initially, because Microsoft had no history in research," Myhrvold says. "Every job offer to these people that I started hiring went to someone at a company or an institution that was more than 100 years old. So they were quite skeptical about the new kid on the block." Myhrvold's first hire—undertaken at the urging of Bell—was Richard F. Rashid, a professor of computer science at Carnegie Mellon University and a developer of the Mach operating system that was the basis for the one that went into the NeXt computer and for Apple's OS X.

The reluctance to come onboard did not last for long. Microsoft went on such an intensive hiring spree that some computer science departments complained about the company robbing them of their best talent. Growing to its current size—with an estimated yearly budget of more than $250 million—Microsoft Research also set up laboratories in Cambridge, England; Beijing; San Francisco; and Silicon Valley. In building an industrial research laboratory, Rashid modeled Microsoft Research loosely after the Carnegie Mellon computer science department. The first order was to keep bureaucracy at a minimum. Researchers can publish papers without first consulting higher-ups—and are given a relatively free hand in spending.

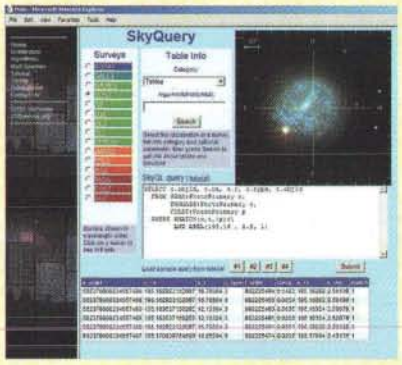
"We don't have budgets for our research projects," Rashid says. "If somebody needs something, they get it, and if they don't need something, they're not supposed to ask. And if they ask for a lot of things they don't need, they'll be fired." Rashid, whose quiet but firm demeanor bespeaks his years as an academic, says he keeps no formal metrics to measure researcher productivity. But he points to the number of papers published at places such as SIGGRAF, the graphics conference, where as many as one quarter of the papers

WORK ON ANYTHING (BUT NO JETÉS)

The scope of research at Microsoft ranges from theoretical mathematics to applied systems that may point to how the company plans to go up against Google in search engines. A few examples follow:

Susan Dumais, a mathematician and psychologist who is a veteran of both Bell Labs and Bellcore, has devised a new approach for tracking down digital files. Called Stuff I've Seen, it creates a unified and searchable index of documents that have been previously referenced by a user, whether a Web page, e-mail, spreadsheet or any other file. Now in early testing among 1,500 users at Microsoft, it may well show up in a new Microsoft search engine or operating system. "It's a blast being here," Dumais says, adding: "It's amazingly seductive to ship what you've done to hundreds of millions of people."

James Gray, 1998 winner of the Turing Award, one of the highest honors in computer science, helped to devise a Web-based tool, SkyQuery.Net (*right*), that lets an astronomer submit a single query to archives of data from optical and radio telescopes, allowing data on objects located in the same areas of the sky to be correlated. It is a prototype for a World Wide Telescope that may one day do the same across all such astronomy archives and may shed light on the problems of data mining for large commercial databases.



Michael H. Freedman, a 1987 winner of the Fields Medal in mathematics, is working on a radically new approach to quantum computation that relies on an excited state of matter (a quasiparticle) that has yet to be discovered. When first recruited by Nathan Myhrvold in 1996, Freedman asked his soon-to-be boss whether he could work on anything he wanted. "Maybe not ballet dancing," Myhrvold told him.

SLOAN DIGITAL SKY SURVEY

have come from Microsoft Research in a given year, topping any other institution.

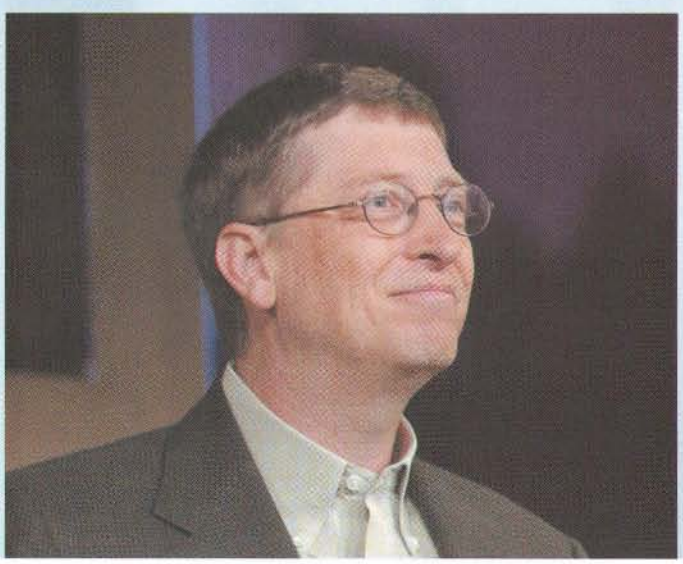
No longer does Rashid have to crack the joke that putting the words "Microsoft" and "Research" together creates an oxymoron. The company can supply a long list of products that incorporate programming code or engineering designs from the research side: ClearType, which improves display resolution; a text-to-speech tool to convert a Word document into spoken language; a grammar checker; and optimization tools to speed loading time and memory performance. "Within the first five years [of its start in 1991], every single product had some code or technology from Microsoft Research," Myhrvold says. Of course, there have also been flops. Talisman, an advanced graphics-rendering system, never got to the marketplace in 1997 when a hardware manufacturer failed to deliver a chip on schedule that incorporated Microsoft's graphics algorithms, although parts of the technology made their way into other company products. And, to be sure, many computer users still guffaw when remembering Clippy, the obnoxious paper clip Help icon hovering over the desktop.

Some outsiders, though, express disappointment that the company has not done more. In its role as the dominant presence in software, Microsoft, they lament, still has a long way to go to improve the experience of the average computer user. "Microsoft has had some of the brightest computer scientists the world has ever produced, people who understand security better than anybody, and yet they fail to think fundamentally about an entirely new way that computers could run that makes them infinitely more secure and virus-free," notes John Seely Brown, former director of Xerox PARC. "For some reason, they haven't been tackling some of the most fundamental problems, and I'm confused by that." Brown says he expects more from the industry's leading software vendor: "We have to count on them now to make the really fundamental breakthroughs that are going to transform computing, not in terms of things at the periphery but in terms of things that make systems bulletproof."

This skepticism is echoed by others who also question Microsoft Research's impact. "I see individual islands of excellence but nothing that's moved the needle for Microsoft," comments Dick Lampman, director of Hewlett-Packard Laboratories. Bill O'Leary, director of communications for IBM Research, says

Talking to Bill

Bill Gates spoke recently with *Scientific American*'s Gary Stix on topics ranging from artificial intelligence to the value of basic research. Excerpts appear below. An extended version of the interview can be accessed at ScientificAmerican.com (www.sciam.com).



KIM KULISH *Corbis*

Scientific American: Do you plan to continue your commitment to research?

Bill Gates: Yes, our research has had a phenomenal payoff for us and for our users. We are dependent on our research, whether it's for ensuring ultrareliability [or] deep security or for making it simple to deal with all the information that we've got. It's the advances out of our research lab that make us optimistic that we'll be solving these tough problems.

SA: Some critics have said that there is an unbelievable collection of talent here but that there have not been achievements on the order of things like the transistor. Do you see any validity in that?

BG: Well, we do software. And if you look at the papers at SIGGRAPH [a computer graphics conference] and the proportion coming out of our one lab, you see us in many different areas. We wish there were other labs doing more. We are a very high percentage of the nonuniversity work being done in many of these fields. Typically in the computer field, most of the companies don't have long-term research. They just don't.

Take what we've done in machine translation—no, that's not as good as the transistor, but it's pretty phenomenal. The stuff we're doing with speech, pretty phenomenal. Electronic ink. Software reliability. If we weren't able to prove [test and validate] programs, we wouldn't be

that Microsoft has yet to build a close enough connection between researchers, on the one hand, and product developers and customers, on the other, a prerequisite for transferring ideas and prototypes into actual products.

For years, Microsoft's detractors have accused it of adopting technologies others had invented and using its position in operating-system software to become dominant in a new market. Rashid claims that Microsoft Research serves as proof that this assertion now rings false. "We're pushing the state of the art in many, many fields, whether it's computer vision, graphics or machine translation." Microsoft, he says, also has established a "dating service" to ensure that products get transferred from researchers to developers. One objective criterion lends support to a few of Rashid's arguments. In an analysis of 2003 data by intellectual-property consultant CHI Research, Microsoft ranked higher than any other top patenting computer-industry firm, including IBM and Hewlett-Packard, in a "science linkage" index that examines how often a business cites scientific papers in its own patents, a measure of whether its technology is based more on scientific advances than that of its rivals.

Doing both basic and applied research—an option open only to market leaders like Microsoft—may supply the preconditions for the vaunted serendipity that leads to breakthroughs. Certainly the aggregation of intellectual firepower has produced a particularly energized work environment. Jim Blinn, a MacArthur "genius award" winner who accounted for a large percentage of the algorithms deployed in the early years of the computer graphics field, had stopped that work in his post at the California Institute of Technology. For more than 10 years before arriving at Microsoft Research in 1995, he had been producing educational animations. But at Microsoft, he has now returned to basic studies, looking at the geometry of how shapes are represented and manipulated. "I'm having a great time," Blinn says. "I'm working on stuff I wouldn't have had the time or resources to do in a university department."

Microsoft appears to have succeeded in building a haven for leading computer science. But channeling and shaping the creative energies of researchers such as Blinn into technology relevant to the corporation has been a challenge for managers such as Rashid since the first industrial laboratories started forming more than a century ago.

able to get the Internet to achieve its potential. An investment of the size we're making will only be judged 20 years from now.

SA: Do you see continued relevance in the concept of artificial intelligence [AI]? The term is not used very much anymore. Some people say that's because it's ubiquitous, that it's incorporated into lots of products. But there are plenty of neuroscientists who say that computers are still clueless.

BG: And so are neuroscientists [*laughter*]. No, seriously, we don't understand the plasticity of the neurons. How does that work? We don't understand why a neuron behaves differently a day later than before. What is it that the accumulation of signals on it causes?

There is a part of AI that we're still in the early stages of, which is true learning. Now, there's all these peripheral problems—vision, speech, things like that—that we're making huge progress in. If you just take Microsoft Research alone in those areas, those used to be defined as part of AI. Playing games used to be defined as part of AI. For particular games it's going pretty well, but we did all this work without a general theory of learning. I am an AI optimist. We've got a lot of work in machine learning, which is sort of the polite term for AI nowadays because it got so broad that it's not that well defined.

SA: Are enough people going into the computer sciences?

BG: That was the big theme of my recent tour to colleges throughout the U.S. It's a paradox that this is the most exciting time in computer science and these are the most interesting jobs. You can see the work being done to really improve the creativity and effectiveness of hundreds of millions of people. These jobs should be way more interesting than even going to Wall Street or being a lawyer—or, I can argue, than anything but perhaps biology, and there it's just a tie.

And yet the number of people going in has gone down, and it's hard to measure whether we are getting the best and brightest. There is this huge disparity. We're getting the best and brightest in China and India, and the numbers are just going up there. Does that mean that this country will have to let those people come here, or does it mean the good work in the future won't be done here? So we really need a rededication to what's made the U.S. such a leader.

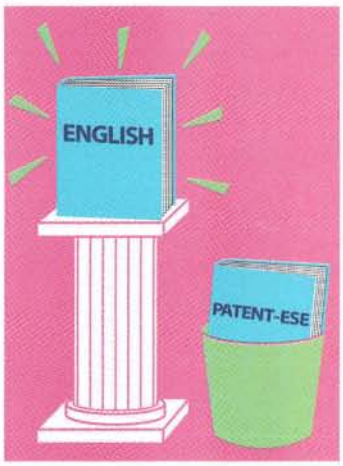
SA: Why are people less attracted to these jobs here?

BG: Oh, it's partly that the bubble burst. It's partly articulating the benefits of the field and the variety of jobs. People have to know that these are social jobs, not just sitting in cubicles programming at night. Our field is still not doing a good job drawing in minorities or women, so we're giving up over half the potential entrants.

The Silent Revolution

An upcoming book deciphers in plain language what ails the patent system By GARY STIX

Ex parte Allen. The doctrine of equivalents. Methods of doing business. Interferences. The First Inventor Defense Act. Reduction to practice. The mental steps doctrine. Disclosure under section 102(e). Derivation under section 102(f). The recapture rule. Laches and estoppel. Graver Tank *v.* Linde Air Products Co. Jepson claims.



The patent bar is a priesthood with its own secret dialect, intelligible only to initiates. Two economists—Adam B. Jaffe of Brandeis University and Josh Lerner of Harvard Business School—have now undertaken to translate for the rest of us the inner workings of the patent process and then to dissect what plagues it. *Innovation and Its Discontents: How Our Broken Patent System Is Endangering Innovation and Progress and What to Do about It* is to be published by Princeton University Press in October. The book describes how two seemingly well-meaning changes made by the U.S. Congress have engendered the current crisis.

In what the authors call a "silent revolution," Congress in 1982 took what appeared to be the relatively mundane decision of assigning all appeals in patent cases to a single court—the Court of Appeals for the Federal Circuit (CAFC). Intended to eliminate "forum shopping" (the attempt by plaintiffs to find the most patent-friendly jurisdiction), the congressional move ultimately resulted in a court whose specialized nature tended to turn it into an advocate of patent holders' rights. The CAFC has issued ruling after ruling that sustains lower-court findings of patent infringement and has fostered the extraction of greater damages from defendants. It has even made it easier for a patentee to shut down a competitor's business before the patent is shown to be valid. And its rulings have held that software, business methods and certain biotechnologies—considered by many to be unpatentable—are eligible to receive patents.

The other major action by Congress came in the early 1990s, when, during the annual budgetary process, it converted the U.S. Patent and Trademark Office from a primarily taxpayer-funded agency to one that survives on the fees it collects. The revamped structure, intended to serve patent applicants in a businesslike manner, created incentives to process patent applications as fast as possible, with little heed to the complexity of a particular application. The two actions, Jaffe and Lerner assert, led to a decline in rigor in the standards by which patents are assessed. The impact of the changes resulted in an explosion in patents granted: annual increases in patenting had nudged along at a rate of less than 1 percent from 1930 to 1982; in contrast, that rate skyrocketed to about 5.7 percent from 1983 to 2002.

Rather than marking a blossoming of innovation, the patent boom has signified a rise in the number of questionable patents, such as, infamously, a Smucker's patent on crustless peanut butter and jelly sandwiches. A broadening of patent coverage has also inhibited research. For instance, some medical investigators, the authors note, have abandoned their programs to study two breast cancer genes because of what they perceive as onerous licensing terms imposed by Myriad Genetics, the holder of the patents on these genes. A concurrent growth in infringement lawsuits creates a situation in which established companies, often with declining market shares but large patent portfolios, file suit against smaller firms, forcing the defendants to pay royalties that crimp their ability to conduct their own research and development. The collective effect has produced what the authors characterize as nothing less than a tax on innovation. SA

Next month this column will describe Jaffe and Lerner's solutions for reforming the patent system.

JENNIFER KANE

Death by Theory

Attachment therapy is based on a pseudoscientific theory that, when put into practice, can be deadly By MICHAEL SHERMER

In April 2000, 10-year-old Candace Newmaker began treatment for attachment disorder. Her adoptive mother of four years, Jeane Newmaker, was having trouble handling what she considered to be Candace's disciplinary problems. She sought help from a therapist affiliated with the Association for Treatment and Training in the Attachment of Children (www.ATTACh.org) and was told that Candace needed attachment therapy (AT), based on the theory that if a normal attachment is not formed during the first two years, attachment can be done later.

According to the theory, the child must be subjected to physical "confrontation" and "restraint" to release repressed abandonment anger. The process is repeated until the child is exhausted and emotionally reduced to an "infantile" state. Then the parents cradle, rock and bottle-feed him, implementing an "attachment."

Candace Newmaker was killed by pseudoscience.

Candace was treated by Connell Watkins, a nationally prominent attachment therapist and past clinical director for the Attachment Center at Evergreen (ACE) in Colorado, and her associate Julie Ponder. The treatment was carried out in Watkins's home and videotaped. According to trial transcripts, Watkins and Ponder conducted more than four days of "holding therapies." On one day they grabbed or covered Candace's face 138 times, shook or bounced her head 392 times and shouted into her face 133 times. When these actions failed to break her, they put the 68-pound Candace inside a flannel sheet and covered her with sofa pillows, while several adults (with a combined weight of nearly 700 pounds) lay on top of her so that she could be "reborn." Ponder is reported to have told the girl to imagine that she was "a teeny little baby" in the womb, commanding her to "come out head first." In response, Candace screamed, "I can't breathe, I can't do it! ... Somebody's on top of me.... I want to die now! Please! Air!"

According to AT, Candace's reaction was a sign of her emotional resistance, calling for more confrontation to achieve emotional healing. ACE (now operating as the Institute for Attachment and Child Development) claims that "confrontation is sometimes necessary to break through a child's defenses and reach the hurting child within." Putting theory into practice, Ponder admonished, "You're gonna die." The girl begged: "Please, please, I can't breathe." She then vomited and cried, "I gotta poop." Ponder instructed the others to "press more on top," on the premise that such children exaggerate their distress. Her mother entreated, "I know it's hard, but I'm waiting for you."

After 40 minutes of struggling, Candace went silent. Ponder rebuked her: "Quitter, quitter!" Someone joked about performing a C-section, while Ponder patted a dog that meandered by. After 30 minutes of silence, Watkins remarked, "Let's look at this twerp and see what's going on. Is there a kid in there somewhere? There you are lying in your own vomit. Aren't you tired?"

Candace wasn't tired; she was dead. The death certificate listed the proximate cause as asphyxiation, and her therapists received the minimum sentence of 16 years for "reckless child abuse resulting in death." The ultimate cause was pseudoscientific quackery masquerading as psychological science. "However bizarre or idiosyncratic these treatments appear—and however ineffective or harmful they may be to children—they emerge from a complex internal logic based, unfortunately, on faulty premises," write Jean Mercer, a psychologist at Richard Stockton College of New Jersey, and Larry Sarner and Linda Rosa of the National Council against Health Fraud in their 2003 analysis, *Attachment Therapy on Trial: The Torture and Death of Candace Newmaker.*

Other children have died after AT as well. The American Psychiatric Association states: "While some therapists have advocated the use of so-called coercive holding therapies and/or 're-birthing techniques,' there is no scientific evidence to support the effectiveness of such interventions." Nevertheless, AT continues to flourish. ATTACh claims to have about 600 members. The numbers may be even higher, Mercer, Sarner and Rosa say, because the practice goes by different labels, including holding-nurturing process, rage reduction, cuddle time and compression therapy (see www.ChildrenInTherapy.org).

By whatever name, AT remains a pseudoscience. We should ban its practice before it tortures and kills children again. SA

Michael Shermer is publisher of Skeptic *(www.skeptic.com) and author of* The Science of Good and Evil.

BRAD HINES

A Transparent Enigma

Low-functioning autistics are not supposed to joke, write or creatively express a rich inner life. But then there's Tito Mukhopadhyay BY MADHUSREE MUKERJEE

At 7 A.M. in a nondescript apartment in Hollywood, Calif., Tito Mukhopadhyay is hunched over his breakfast bowl, spooning milk and cereal into his mouth. His eyes flit around and his hand shakes. When he is finished, his mother, Soma Mukhopadhyay, pulls him off the chair and manhandles him into the shower, dashing in from time to time when he yells for assistance.

TITO MUKHOPADHYAY: ILLUMINATING AUTISM

- His mother, Soma (*above, right*), taught him to write. An advocacy group of parents and educators called HALO (Helping Autism through Learning and Outreach) hopes to formally study her strategy of "rapid prompting."
- Knows English, Bengali and Hindi: "I love language. Even when I could not understand my surroundings, I understood the pattern of language."
- On life: "I believe in absurdism. It is absurd to exist. Just see why we are alive, why we are dead. What is the use of the universe?"

Finally Tito emerges, dressed, to bend over Soma's tiny frame so she can comb his thick black hair. Abruptly he charges out the door and half-walks, half-runs down the hallways until he is outside. Golden sunshine on his face, he flaps and spins his hands with absorption.

Later I ask him: "Would you like to be normal?" In rough but legible script, he scrawls: "Why should I be Dick and not Tito?"

At 15, Tito displays all the signs of classic "low-functioning" autism. Years ago in India, a doctor told his parents that the boy could not understand what was happening around him. " 'I understand very well,' said the spirit in the boy," he related in *The Mind Tree*, a book he penned between the ages of eight and 12. (Tito typically refers to himself in the third person.) Indeed, he wrote about having two distinct selves: a "thinking self—which was filled with learnings and feelings" and an "acting self" that was "weird and full of actions" occurring independently of his thoughts.

Autistic intelligence varies widely, from severe retardation to savant syndrome. Tito combines extreme neurological disability with an ability to write—and so can tell the world of a bizarre internal condition.

Wanting to talk, Tito once stood before a mirror pleading for his mouth to move. "All his image did was stare back," he wrote. Parents often take an autistic's unresponsiveness to be stubbornness; Tito's writings dispel that notion. He has trouble moving his muscles at will, and now he speaks in barely intelligible grunts that his mother must often translate. He "saw himself as a hand or as a leg and would turn around to assemble his parts to the whole," Tito explains of another typical activity, rotation. Spinning his hands helps him to become more aware of bodily sensations.

Conflicting and overwhelming sensory input seems to beset autistics, who respond by shutting off one or another sense at a time, notes neurologist Yorram S. Bonneh of the Weizmann Institute of Science in Rehovot, Israel. Tito, for instance, routinely fails to hear

RANDI BEREZ

and see someone at the same time and so avoids eye contact—a defining characteristic of autism. In 2001 Bonneh and others found that if Tito was presented with a bright red flash and a simultaneous voice saying "blue," he responded, "I saw blue" or "I am confused." He turned out to have a hierarchy of senses: hearing overrode vision, and both extinguished touch. Sometimes he could feel nothing at all with his fingers. Such startling effects as he displayed had hitherto remained hidden, for a low-functioning autistic does not normally cooperate with experimenters.

All the interfering signals lead to "a fragmented world perceived through isolated sense organs," Tito has written. He comprehends the world by reading or when his mother reads aloud to him—physics, biology, poetry. "It is because of my learning of books, that I could tell that the environment was made of trees and air, living and nonliving, this and that," he wrote.

Born in India, Tito learned to communicate through his mother's unrelenting efforts. Living alone with her son in Indian cities that boasted autism specialists (Tito's father worked in a distant town), Soma Mukhopadhyay, who is trained as a chemist and educator, tried every imaginable trick to get her strange child to respond. When one expert said Tito was retarded, she cried bitter tears and went to a different doctor. Her first success with Tito came after she found him staring at a calendar; she pointed at the numbers, saying them out loud. In one heady week before the age of four, Tito learned to add and subtract numbers and compose words by pointing to numbers and letters written on a board.

Because experts suspected Soma to be cueing Tito, she taught him to write. She tied a pencil to his hand and forced it to trace the alphabet until he could do it alone. Still, she observes him with profound intensity and snaps her fingers the moment Tito's thoughts stray—which is all the time during my visit. He seems to be beset by random neural firings. If she didn't intervene, Soma explains, he would write words from a different sentence in the middle of one he had already started.

"The fidelity of the method will be very, very difficult to replicate," predicts Richard Mills of the National Autistic Society in London, who met Tito in Bangalore and introduced him to the Western world. Soma now works with several children in Los Angeles, using her so-called rapid prompting method, reportedly with spectacular success. She communicates using whichever sensory channel is open in a child, and he or she responds by pointing to letters or pictures. Often she enables the pointing by touching a hand or shoulder (according to Tito, touching allows a child to feel the body part and so control it), and she cuts off stray thoughts. Unfortunately, Mills points out, autism is bedeviled by claims of treatments that eventually evaporate, and Soma's method has yet to be scientifically validated.

Even if they can communicate, few autistics are likely to reveal personae anywhere as complex as Tito's. One day, he wrote, things become transparent: "A transparent room, then a transparent ceiling ... and a transparent reflection of myself showing only the rainbow colours of my heart." Experts long believed that autistics lack imagination and introspection. Lorna Wing, also at the National Autistic Society, explains that these qualities are in fact present but impaired—autistics tend to be uninterested in and unempathetic with others.

A popular theory, championed by Uta Frith of the Medical Research Council in London, holds that autistics lack an intuitive "theory of mind"—that is, they cannot automatically perceive what someone else is thinking. Not "getting" deception or nuance, they are straitlaced and humorless. Temple Grandin of the University of Illinois, for instance, is a high-functioning autistic whose phenomenal ability to visualize and to empathize with cows allowed her to design more humane slaughterhouses. In her fascinating book *Thinking in Pictures,* Grandin notes that she can comprehend others and even deceive people. Nevertheless, her understanding comes with sustained intellectual effort: she studies people as primatologists study chimpanzees.

Tito's hierarchy of senses—hearing over vision over touch—leads to a "fragmented world perceived through isolated sense organs."

Grandin's book reads as if she were part robot—Tito's, on the other hand, reads as if he were an unusually creative and perceptive child, albeit one to whom very odd things happen. The "theory of mind" idea fails to apply to Tito, states Michael Merzenich of the University of California at San Francisco. Wing counters that those who use language with ease, as Tito does, indeed perform well on tests of the theory of mind. But even Tito, she argues, has trouble applying his theory of mind to behave appropriately in complex social situations.

During an evening drive to the beach, the conversation somehow turns to Darwin. "You should say autistics are the most evolved of humans," Tito opines. "It is a recent mutation." I protest, startled at such a claim. "Just making fun. Can't I make fun?" he replies abruptly—it was I who didn't get it. After a while he adds that in my story I should "put the fun part, because it tells [about] the theory of mind."

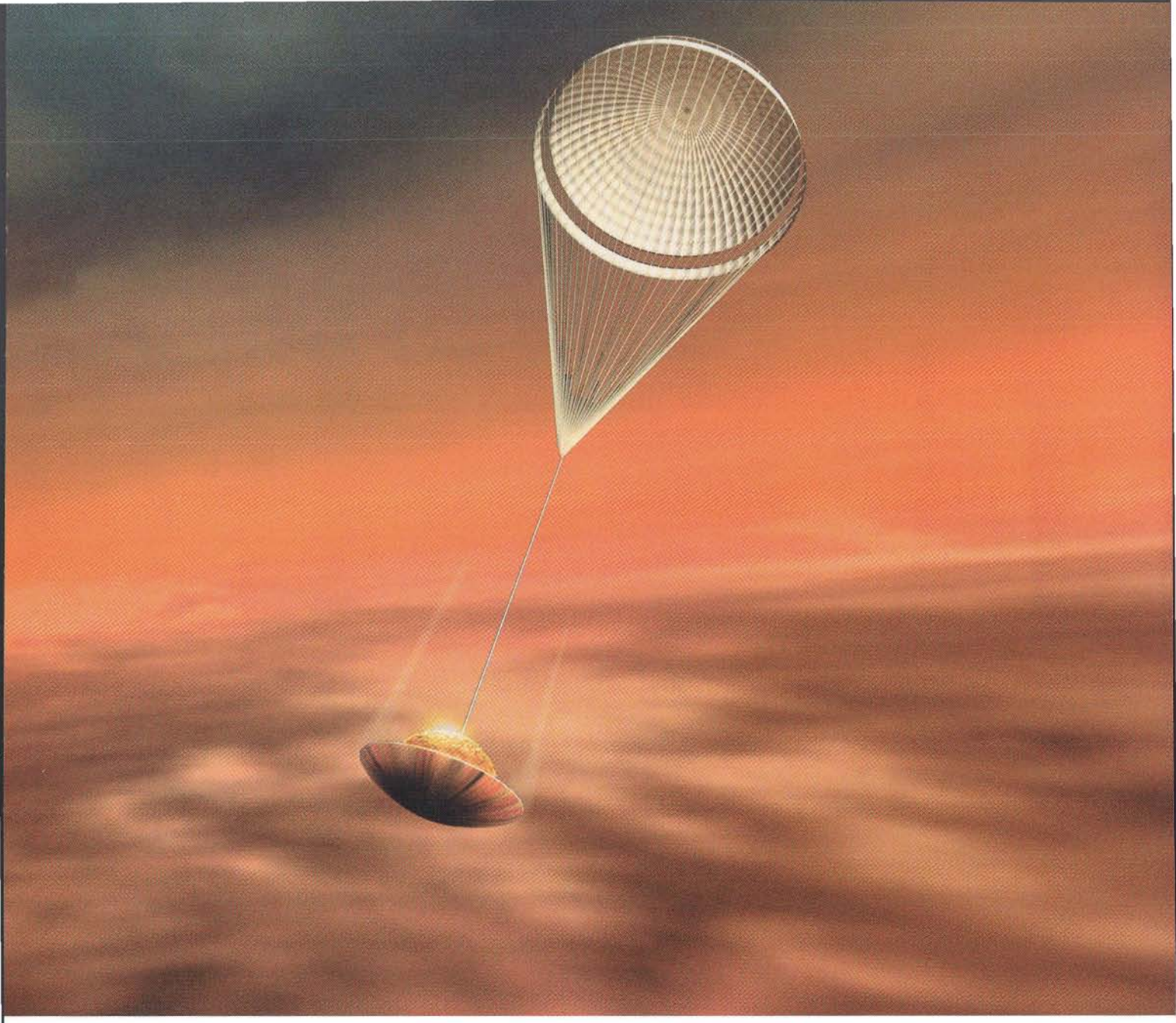
The beach is chilly, breezy and dark, but Tito strides ahead. After calling to him to stop, his mother rolls up his trouser legs. He enjoys "the water, the sound and the air" at the beach, he later explains. "I always like the air." Facing the vast black ocean, Tito stands alone, bare toes dipped into the sand and surf, hands spinning and flapping. SA

Madhusree Mukerjee, a former staff writer, is author of The Land of the Naked People: Encounters with Stone-Age Islanders *(Houghton Mifflin, 2003).*

DESCENT OF THE HUYGENS PROBE into the thick atmosphere of Titan, Saturn's largest moon, will be one of the highlights of the upcoming Cassini-Huygens mission. The analysis of organic chemicals in Titan's atmosphere and on the moon's surface may reveal clues to how life emerged on Earth billions of years ago.

SATURN AT LAST!

DON DIXON



After a seven-year journey, the Cassini-Huygens spacecraft is preparing to unveil the mysteries of Saturn, its rings and its giant moon, Titan

By Jonathan I. Lunine

Early in the morning of October 15, 1997, standing in the dark on the edge of an alligator-infested inlet near Cape Canaveral, Fla., I watched with thousands of others as a tiny flame appeared beneath a rocket illuminated by floodlights on a launchpad several miles away. Only the booster's fiery tail was visible as the rocket ascended through a cumulus cloud and then arced over the ocean, headed for space. The most sophisticated robotic spacecraft ever built, the Cassini orbiter and the attached Huygens probe, were poised atop the launch vehicle, and seven years of interplanetary voyaging lay ahead. I had begun my involvement in the planning of this mission as a graduate student, and I would have to wait until the middle of my scientific career to see its culmination: the first prolonged exploration of the Saturnian system.

This July the Cassini-Huygens spacecraft is expected to go into orbit around the solar system's second-largest planet. Researchers have been eagerly awaiting this day ever since the flyby missions—Pioneer 11 and Voyagers 1 and 2—piqued their interest in Saturn more than 20

years ago. Although the planet is smaller than Jupiter and its surface is much less dramatic in appearance, Saturn may hold vital clues to the long-term evolution of all the gas-giant planets. Saturn's retinue of moons includes 30 icy satellites and one planet-size body, Titan, which has a dense atmosphere that fascinates scientists because it could reveal how life arose on Earth. Researchers also wish to discover how Saturn's rings formed and how the planet's powerful magnetic field affects the icy moons and the upper atmosphere of Titan.

Scientists are hoping that Cassini-Huygens repeats the success of the Galileo spacecraft, which revolutionized our understanding of Jupiter and its moons during its eight years in orbit. Yet there are fundamental differences between these two outer-planet missions. Whereas Galileo released a probe to investigate Jupiter's atmosphere, the Cassini orbiter will send the Huygens probe to Titan, not Saturn. And unlike Galileo, Cassini-Huygens is a truly international effort: although NASA built the Cassini orbiter and is managing the mission, the European Space Agency (ESA) developed the Huygens probe, and the science teams for all the spacecraft instruments include Europeans and Americans.

The Cassini orbiter and Huygens probe form one of the biggest PLANETARY SPACECRAFT ever built.

Birth of a Mission

BECAUSE SATURN IS NEARLY twice as far from the sun as Jupiter is—1.4 billion kilometers versus 780 million kilometers—it has always seemed more mysterious. Compared with Jupiter, Saturn has fewer visible belts and zones defining wind patterns in its atmosphere. Saturn's magnetosphere—the region dominated by the planet's magnetic field—is much quieter than Jupiter's, which causes radio noise that is easily detectable from Earth. Astronomers had discovered an atmosphere around Titan in 1943, but little else was known about it or Saturn's other moons until the Space Age. To earthbound astronomy enthusiasts, Saturn was the serenely beautiful and mysterious counterpart to the overtly violent Jupiter, floating in a distant, frigid realm.

The first spacecraft to visit Saturn, Pioneer 11, was a relatively simple probe that flew by Jupiter in 1974 and raced past Saturn in 1979. Its instruments detected a previously unknown ring of Saturn (the F ring), remotely measured the properties of the gas giant's atmosphere and gauged the strength and geometry of the planet's magnetic field. Voyagers 1 and 2, which flew by the Saturnian system in 1980 and 1981, respectively, possessed more sensitive imaging systems and spectrometers. The spacecraft discovered unexpected structures in Saturn's rings—dark radial streaks that cut across the rings like spokes extending from a wheel—which apparently result from the electromagnetic levitation of dust above the ring plane. This phenomenon and other measurements indicated that the rings are composed of objects ranging in size from boulders down to tiny dust particles.

The Voyagers also imaged parts of the surfaces of many of Saturn's icy satellites, which showed varying degrees of melting and resurfacing. But it was Titan that arguably provided the most exciting discoveries. Voyager 1 flew as close as 4,000 kilometers to this moon, which is the second largest in the solar system (after Jupiter's Ganymede). Titan's thick orange haze prevented the craft's cameras from observing any features on the surface, but other instruments measured atmospheric temperature and pressure, and determined that nitrogen is the most abundant gas, followed by methane.

The spacecraft revealed that the dynamics of Titan's atmosphere are eerily akin to those of Earth. Nitrogen dominates both atmospheres, but on Titan methane plays the meteorological role that water plays on Earth. Methane is also at the heart of organic chemical reactions that begin in Titan's upper atmosphere with the breakup of its molecules by ultraviolet radiation from the sun. Scientists believe that this atmospheric cycle may include the raining of liquid hydrocarbons, which could accumulate in lakes or oceans on the moon's surface. The surface temperature—about 94 kelvins, or –179 degrees Celsius—is far too cold for liquid water, but conditions are just right for pools of liquid hydrocarbons. Life as we know it probably could not evolve on Titan, but an analysis of the organic chemical cycles on this moon could provide clues to how life emerged in Earth's early history.

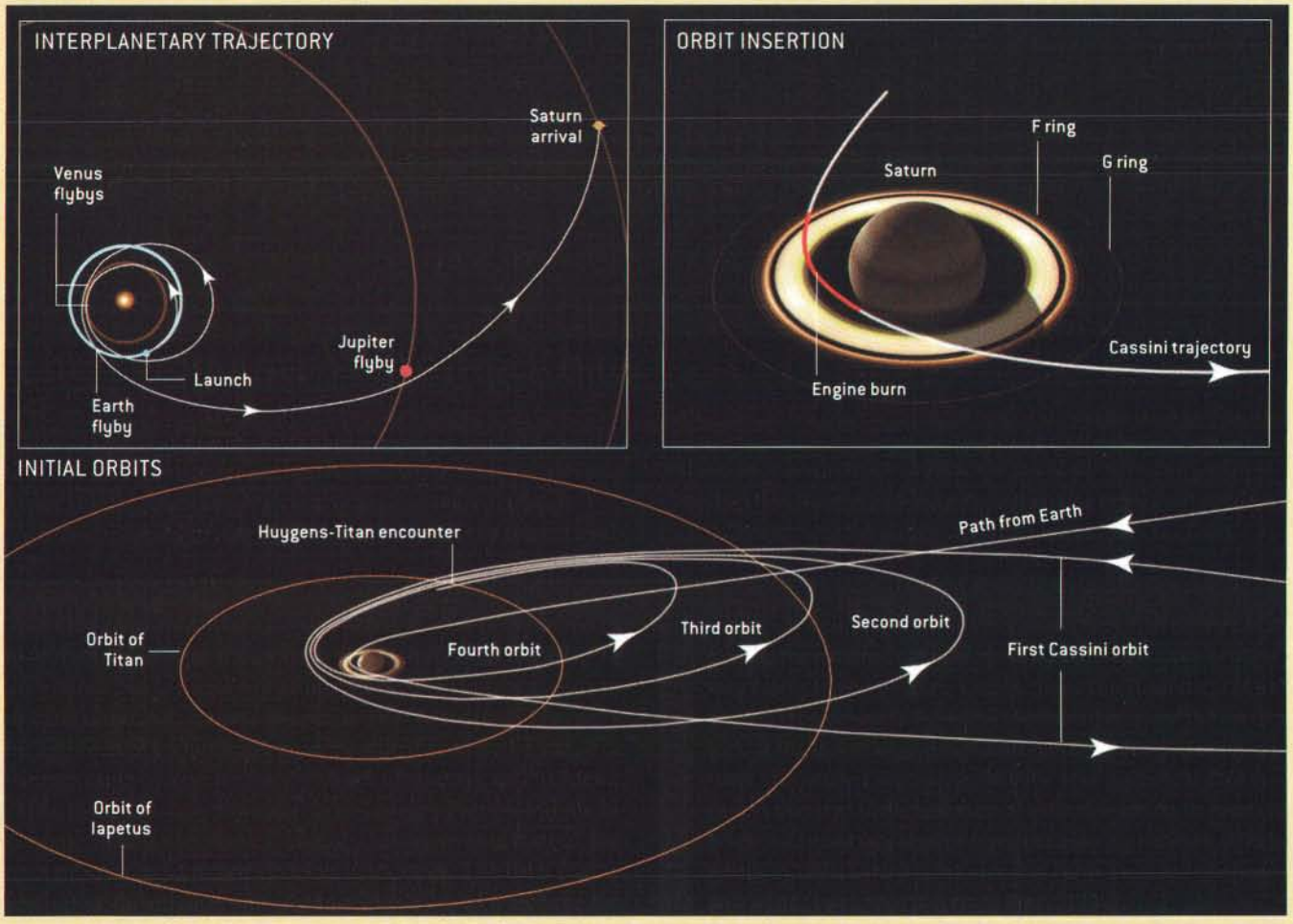
The Voyager results encouraged researchers to contemplate developing an orbiter that could conduct an extended investigation of the Saturnian system. In the early 1980s, however, funding for planetary exploration was limited, so officials from NASA and the ESA began to consider combining their resources. In 1982 and 1983 teams of European and American scientists met to draw up plans for future cooperative exploration of the solar system, and a mission to the Saturnian system was high on their list.

Overview/*Mission to Saturn*

- Launched in 1997, the Cassini-Huygens spacecraft is expected to go into orbit around Saturn this July, beginning a four-year investigation of the planet's atmosphere, moons, rings and magnetic field.
- In December the Cassini orbiter will send the Huygens probe toward Titan, Saturn's largest moon. During a three-hour descent, the probe will study Titan's atmosphere and surface, which may be covered with lakes or seas of liquid hydrocarbons.
- By shedding light on the processes that shape planetary atmospheres, surfaces and rings, the mission promises to revolutionize our understanding of the solar system.

The Long and Winding Road

The Cassini-Huygens spacecraft has already traveled more than three billion kilometers to reach the Saturnian system. Since its launch in 1997, the craft has conducted four gravity assists, swinging by Venus (twice), Earth and Jupiter to boost its velocity (*top left illustration*). On July 1, Cassini will speed through the gap between Saturn's F and G rings and fire its engine in reverse as it makes its closest approach to the planet (*red line in top right illustration*). This maneuver will slow the craft enough to put it into an elliptical orbit (*bottom illustration*). Subsequent engine firings will adjust the orbit to prepare for the Huygens probe's encounter with Titan.



An Amazing Journey

ALTHOUGH IT WAS CLEAR that a key component of the mission would be an orbiter designed to investigate Saturn's atmosphere, rings, moons and magnetosphere, debate centered on whether to drop an atmospheric probe into Saturn or Titan, or both bodies. The last alternative was too expensive. The planners eventually chose Titan because of the intriguing Voyager findings about its atmosphere. By 1985 the ESA had come up with novel designs for an entry probe that could navigate Titan's dense but low-gravity atmospheric environment. Agency officials ultimately named the probe after Christiaan Huygens, the 17th-century Dutch astronomer who discovered Titan. The orbiter, built by the Jet Propulsion Laboratory in Pasadena, Calif., took its name from the 17th-century French-Italian astronomer Jean Dominique Cassini, who discovered four of Saturn's moons and a major division in its rings. The total cost of developing the mission—more than $3 billion, of which the Europeans contributed about 25 percent—is high compared with most planetary missions but comparable to that of other large programs such as the Hubble Space Telescope.

The Cassini orbiter and Huygens probe together form one of the biggest and heaviest planetary spacecraft ever built, with 12 scientific instruments on the orbiter and six on the probe [*see*

THE AUTHOR

JONATHAN I. LUNINE is an interdisciplinary scientist for the Cassini-Huygens mission to the Saturnian system. A professor of planetary sciences and physics, Lunine chairs the Theoretical Astrophysics Program at the University of Arizona. His research interests include the formation and evolution of planets and planetary systems, the nature of organics in the outer solar system, and the processes that lead to the formation of habitable worlds. He received his Ph.D. in planetary science from the California Institute of Technology in 1985. Lunine is the author of *Earth: Evolution of a Habitable World* (Cambridge University Press, 1999).

DON DIXON

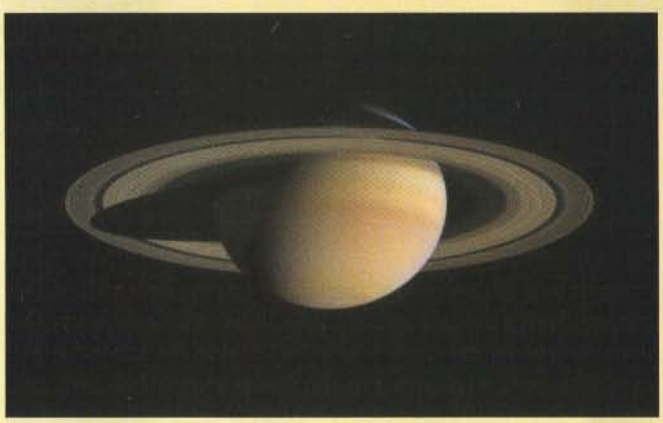
The Beautiful and Mysterious Saturnian System

The target of the Cassini-Huygens mission is perhaps the most fascinating locale in the solar system: a gas-giant planet surrounded by massive rings, a powerful magnetic field, an enormous moon and dozens of smaller icy satellites. The descriptions below highlight some of the things that scientists hope to learn about these bodies.

Saturn

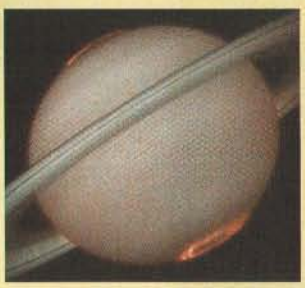
Diameter: 120,536 kilometers
Distance from the sun: 1.4 billion kilometers

Cassini produced this image of Saturn in March, when the spacecraft was about 56 million kilometers from the planet. Roughly one third the mass of Jupiter, Saturn consists primarily of hydrogen and helium, with smaller amounts of methane and ammonia. Saturn emits an unexpectedly large amount of heat. Laboratory experiments and theory suggest that the cause of the excess heat may be friction from droplets of liquid helium sinking through lighter liquid hydrogen toward the center of the planet. If this hypothesis is correct, helium should be relatively depleted in Saturn's atmosphere. Voyager 1 measured the helium abundance indirectly with its infrared spectrometer, but the result was ambiguous. The Cassini orbiter's infrared spectrometer will gauge the helium abundance more accurately. Cassini will also get a better determination of the heat emitted by Saturn. These measurements could indicate whether the helium and hydrogen in the planet's deep interior are indeed separating.



Magnetosphere

Extends up to 1.5 million kilometers toward the sun and 10 to 100 times that distance away from the sun



Saturn's magnetosphere is more symmetrically arrayed than Jupiter's and generates much less radio noise. Why is this so? One possible reason is that Saturn's interior may be less electrically conductive than Jupiter's. Yet the ions trapped in the planet's magnetic field are still powerful enough to modify the surfaces of the icy satellites, erode Titan's atmosphere, strip away small particles from the rings and make beautiful auroral displays above Saturn's poles, shown here in a Hubble Space Telescope image. Cassini's investigation of these phenomena will deepen our understanding of all the complex magnetospheres in the solar system, including the one surrounding Earth.

Rings

Radii of ring orbits: From 67,000 kilometers (inside edge of D ring) to 483,000 kilometers (outside edge of E ring)

Why are the rings of Saturn, shown here in an image taken by Voyager 2 in 1981, so much more dramatic and massive than those of the other giant planets in our solar system? A better

NASA/JPL/SPACE SCIENCE INSTITUTE (*Saturn*); J.T. TRAUGER NASA/JPL (*magnetosphere*)

inset in box on page 32]. Fully fueled, Cassini-Huygens weighed about 5,500 kilograms and stood 6.8 meters tall. Because Cassini had to travel nearly twice as far as Galileo, the spacecraft required a much larger and more robust communications system and antenna (provided by the Italian Space Agency), greater amounts of fuel for maneuvering, and more electrical power. Like Galileo, Cassini is powered by the natural decay of the radioactive element plutonium, which generates heat that is then converted to electricity.

Although Cassini-Huygens was launched on the most powerful unmanned rocket available—the U.S. Air Force's Titan 4B booster with a Centaur upper stage—the spacecraft weighed too much to be sent directly to Saturn. Following the lead of previous missions to the outer solar system, Cassini gained the necessary velocity through a sequence of gravity assists—maneuvers that accelerate a spacecraft by swinging it close to a planet. Between 1998 and 2000 Cassini flew by Venus (twice), Earth and Jupiter. During its December 2000 flyby of Jupiter, Cassini examined the giant planet's magnetosphere from its outer reaches while the Galileo spacecraft took measurements from its closer orbital vantage point—the first time such simultaneous observations had ever been made. These studies revealed that Jupiter's magnetosphere is lopsided, with an unexpected abundance of ions and electrons escaping from one flank. Cassini also produced a remarkable set of images of Jupiter revealing the planet's turbulent atmosphere in extraordinary detail.

The long interplanetary journey provided another benefit: time for NASA and the ESA to modify the mission in response to an unforeseen problem. In 2000 mission planners detected a design flaw when testing the communications system that will enable the Cassini orbiter to receive scientific data from the Huygens probe as it descends to Titan's surface. (The data will then be relayed to Earth.) The radio receiver on the orbiter could not recover the data during a test that simulated the Doppler frequency shift that would occur during the descent. After studying the problem for months, the space agencies came up with a solution: change the planned trajectory to reduce the relative velocity between the orbiter and the probe, which will minimize the Doppler shift.

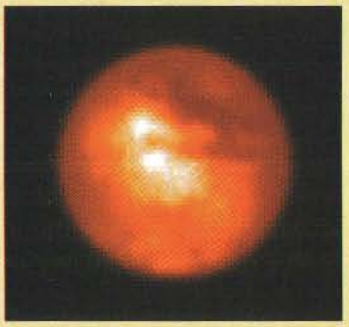
Cassini's first close encounter with the Saturnian system will

understanding of the rings' structure and evolution could provide the answer. Are the rings as old as Saturn, or are they ephemeral? Cassini's cameras and spectrometers will probe the ring structure much more thoroughly than previous missions did. Also, Cassini's antenna will beam radio signals through the rings toward Earth to provide details on the properties of the ring particles. The mission team will look for more evidence of the electromagnetic lifting of dust particles that was first seen by Voyager [*dark streaks that cut across the rings*]. This research may help scientists understand planet-forming processes in the vastly larger debris disks that surround newborn stars.

Titan

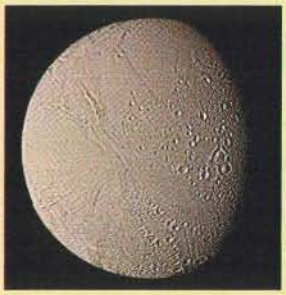
Diameter: 5,150 kilometers
Distance from Saturn: 1.2 million kilometers

A satellite slightly bigger than Mercury with an atmosphere denser than Earth's, Titan—shown here in an image taken by the Keck II telescope—is a world that rivals Earth in climatic and chemical complexity, with one big exception. The temperature at the surface, about –179 degrees Celsius, makes it highly unlikely that life exists there. But heat from the moon's interior or from comet impacts may have intermittently stimulated organic chemical reactions on the surface at certain times in its history. Indeed, large comets striking Titan will create kilometer-size pools of liquid water that may persist—under a thin crust of ice—for hundreds of years, or longer if the antifreeze ammonia is mixed in. Organic compounds trapped in this pool could evolve from simple hydrocarbons and nitrites into amino acids, purines, sugars and other building blocks of life. How this happened on Earth cannot be determined by examining our home planet, because the evidence was destroyed by life itself long ago. But on Titan, the signatures of these transient reactions may be preserved on the moon's surface as variations in the appearance of organic deposits, which can be detected by Cassini's imagers and spectrometers.



Icy satellites

Diameter: from 20 kilometers (for Pan, the smallest measured moon) to 1,528 kilometers (for Rhea, the largest after Titan)
Distance from Saturn: from 133,600 kilometers (for Pan, the closest) to 23 million kilometers (for Ymir, the farthest)



With the exception of Titan, Saturn's moons are all much smaller than the four Galilean satellites of Jupiter, and their density does not follow the same pattern. (The density of the outer Galilean moons is lower than that of the inner ones, indicating a higher ice content.) Saturn's moons are also very different from one another. The highly smooth Enceladus, pictured at right in a Voyager 2 image, shows evidence of very extensive resurfacing in its recent past, a phenomenon usually associated with much more massive satellites. In contrast, Iapetus has a dichotomous surface: the side of the moon facing its direction of orbital motion is much darker than its other side. To shed light on these mysteries, Cassini will study several of the satellites at close range with its imagers, spectrometers, particle detectors and radar.

NASA/JPL/SPACE SCIENCE INSTITUTE (*rings*); M. BROWN, A.H. BOUCHEZ AND C.A. GRIFFITH *California Institute of Technology and W.M. Keck Observatory* (*Titan*); NASA/JPL (*Enceladus*)

be its June 11 flyby of Phoebe, a satellite that travels in an irregular, elliptical orbit about 13 million kilometers from the planet. Cassini will pass within 2,000 kilometers of the 220-kilometer-wide moon, which intrigues scientists because it may be a remnant of the primordial material that formed the rocky cores of the outer planets more than 4.5 billion years ago. Three weeks later, on July 1, Cassini will approach Saturn from below the ring plane, crossing through the wide gap between the F and G rings. To slow the spacecraft enough to allow it to go into orbit, it will fire its engine for 97 minutes in the opposite direction of its travel. During the engine burn, Cassini will make its closest approach to Saturn, coming within 18,000 kilometers of the gas giant. If all goes as planned, this maneuver will put Cassini into a highly elliptical orbit that will later be adjusted by subsequent engine firings [*see bottom illustration in box on page 29*].

Descending to Titan

OVER THE FOLLOWING six months Cassini will fly by Titan twice to study the atmosphere and surface of the giant moon and to prepare for the Huygens mission. On December 25 Cassini will release the Huygens probe, which will coast toward Titan for three weeks. On January 14, 2005, the battery-powered probe will enter the moon's atmosphere, which extends some 1,000 kilometers above the its surface, or about 10 times higher than Earth's atmosphere [*see main diagram in box on next page*]. A saucer-shaped heat shield will protect the craft from the high temperatures of atmospheric entry. At about 170 kilometers above the surface, the probe will deploy parachutes to slow and stabilize its descent. As Huygens floats through the orange haze, the probe's Gas Chromatograph and Mass Spectrometer (GCMS) will analyze the composition of the atmosphere. Another instrument will collect and vaporize solid particles so that they can also be identified by the GCMS. At the same time, the probe's Descent Imager and Spectral Radiometer (DISR) will take pictures of the methane clouds so that researchers can determine their size and shape.

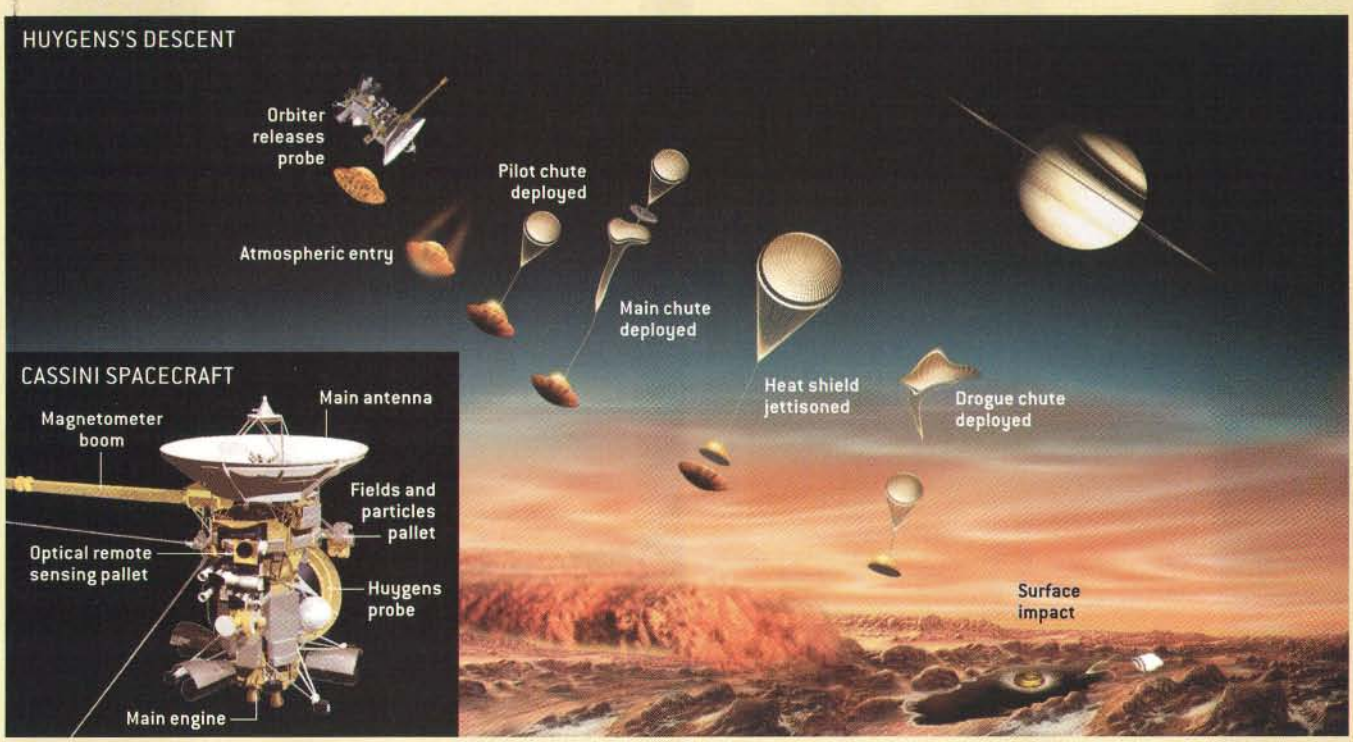
When the probe drops to an altitude of about 50 kilometers, the DISR will begin taking panoramic views of the landscape below. In the last few hundred meters of the descent, a white-light lamp on the probe will illuminate the surface—

Emissary to Titan

On December 25 the Cassini orbiter will release the 320-kilogram Huygens probe, and on January 14, 2005, the probe will enter Titan's atmosphere at a speed of about 20,000 kilometers an hour. When the probe is about 170 kilometers above the surface, parachutes will slow its descent and the heat shield will drop off, allowing the probe's scientific instruments to analyze the moon's atmosphere and surface. The probe will transmit the data to the Cassini orbiter, which will relay the signals to Earth.

The Cassini spacecraft (*inset*) will also study Titan during a series of flybys. The orbiter's Optical Remote Sensing pallet includes two cameras and an array of spectrometers. The Fields and Particles pallet holds several instruments that will examine Saturn's magnetosphere, the region dominated by the planet's magnetic field. Some devices will detect charged particles swirling through the field; others will measure streams of dust, analyze particles ejected from the icy satellites by collisions with fast-moving ions, and directly sample the uppermost atmosphere of Titan as Cassini sweeps within 1,000 kilometers of the moon's surface. A magnetometer mounted on an 11-meter boom will reveal the strength and shape of Saturn's magnetic field.

Cassini's four-meter-wide communications antenna will also function as a radar. The dish antenna can bounce pulses of radio energy against solid bodies and receive the reflected signals, which detail the shape and roughness of the surface. This radar imaging will be able to pierce Titan's atmosphere and map the moon's surface. In addition, the radar system will measure the microwave energy emanating from Titan, revealing the temperature of its surface and atmosphere. Finally, the communications antenna can probe the atmospheres of Saturn and Titan by beaming radio signals through them toward Earth.



which is normally a muddy red because the atmosphere absorbs the blue frequencies of sunlight—allowing the DISR to do a spectral analysis of the surface composition. Throughout the descent, shifts in the frequency of the probe's radio signal will be monitored to infer the strength of Titan's winds, and the Huygens Atmospheric Structure Instrument (HASI) will measure temperature, pressure and electrical fields that could indicate the presence of lightning. The entire descent will last between two-and-a-half and three hours.

Although the primary goal of the Huygens probe is the investigation of Titan's atmosphere, and no provision has been made for guaranteeing survival on landing (which would have been too costly), scientists are keenly interested in the nature of the moon's surface. Is it covered with liquid hydrocarbons? Does it show evidence of geologic activity or organic chemical evolution? Or is Titan simply an icy satellite pocked with craters? To help answer these questions, the probe carries a Surface Science Package (SSP), which will emit sound waves in the final stage of the descent to gauge the roughness of the surface. HASI will make similar measurements using radar signals.

At impact, which will occur at the relatively gentle speed of a few meters per second, accelerometers on the probe will transmit data very rapidly through the SSP to determine whether the surface is hard, snowy or liquid. Should the probe survive the landing, an additional three to 30 minutes of data could be transmitted to the Cassini orbiter before it flies over the moon's horizon. If Huygens lands in a hydrocarbon lake or ocean, the SSP could measure the liquid's temperature, density and other

DON DIXON

properties. The sensors could also gauge the speed of sound through the liquid and perhaps determine its depth. Meanwhile the DISR would take images and the GCMS would try to analyze the hydrocarbons. The Huygens probe is designed to float on liquid hydrocarbons, even though these chemicals are significantly less dense than water.

A Four-Year Tour

AFTER HUYGENS'S DESCENT, the Cassini orbiter will continue to study Titan during its four-year tour of the Saturnian system. Over this period, Cassini will orbit Saturn 76 times, and most revolutions will include close flybys of Titan. Each encounter will also reshape Cassini's orbit, enabling the craft to get close-up views of Saturn's other satellites and its rings, as well as sample different parts of its magnetosphere. Unlike Galileo or Voyager, the Cassini orbiter has no moving platforms for pointing its instruments; to reduce development costs, the devices were fixed to the cylindrical body of the spacecraft. As a result, the mission scientists must carefully plan their observations, because not all the instruments can view the same target simultaneously.

The science to be done in the Saturnian system is so extensive that it can only be summarized in this article [*see box on page 30*]. My own interests focus on Titan. In addition to the issue of whether complex organic chemicals have evolved on Titan's surface, researchers have posed a raft of questions about this world. On Earth, water drives the reshaping of the surface and the exchange of energy and mass between the surface and the atmosphere; on Titan, methane plays this role. But because the methane in Titan's atmosphere is continuously depleted by photochemical reactions caused by the sun's ultraviolet radiation, the compound must somehow be resupplied from the moon's surface or interior or perhaps from comet impacts. The present abundance of methane on Titan, as measured by Voyager, seems to be at a critical point—just enough to allow methane clouds and rain to form. But the concentration is not high enough to allow pure liquid methane at the surface; methane raindrops would evaporate before hitting the ground. If seas exist on Titan, they most likely consist of liquid ethane, a product of the photochemical reactions occurring in the moon's atmosphere, combined with dissolved methane.

Understanding where the methane comes from and where the products of its photochemistry go are among the most fundamental questions that the Cassini-Huygens mission can answer. Are methane and ethane mixed together in hydrocarbon lakes or seas on Titan's surface? New data from the Arecibo radio telescope in Puerto Rico seem to hint that this is the case, but only the Cassini orbiter and the Huygens probe can provide confirmation. If the spacecraft find no evidence of lakes or seas, then perhaps Titan has lacked enough methane and ethane to form them throughout most of its history. If so, the current composition and bulk of the moon's atmosphere—sustained by the greenhouse warming of methane—may be a fluke caused by a recent comet impact or an upheaval from the moon's interior. Finally, planetary scientists are eager to learn where Titan's nitrogen and methane originated and why it is the only moon in the solar system that possesses a dense atmosphere.

All of the spacecraft's instruments will be required to address these questions. The orbiter's imagers, spectrometers and radar, which will be able to see through Titan's thick haze, will look for hydrocarbon seas as they map the moon's surface. Other instruments will examine the interaction of Titan's atmosphere with charged particles from Saturn's magnetosphere. Radio signals beamed through the moon's atmosphere will reveal how much the temperature varies by latitude and altitude. Combining these results with the images from the orbiter and the Huygens probe may help determine the extent of methane precipitation. The probe will also provide direct temperature and pressure readings, along with images of the methane clouds. Furthermore, measurements of two key atmospheric characteristics—the abundance of methane containing deuterium and the ratio of nitrogen to the noble gases argon and krypton—could indicate the possible sources of the moon's methane and nitrogen.

Titan fits the definition of a MYSTERIOUS WORLD better than any other body in the solar system.

The mission team will probably announce a burst of discoveries after Cassini's first flybys of Titan and the Huygens probe descent and then a steady stream of new findings as the orbiter continues to study the giant moon. As with any mission to a strange, new world—and Titan fits the definition of a mysterious world better than any other body in the solar system—no single exploration will answer every question. Titan may prove interesting enough that scientists might propose follow-up missions to send balloons, airships and landers into its dense atmosphere. The long journey of discovery begun by the Cassini-Huygens spacecraft is not likely to end anytime soon. SA

MORE TO EXPLORE

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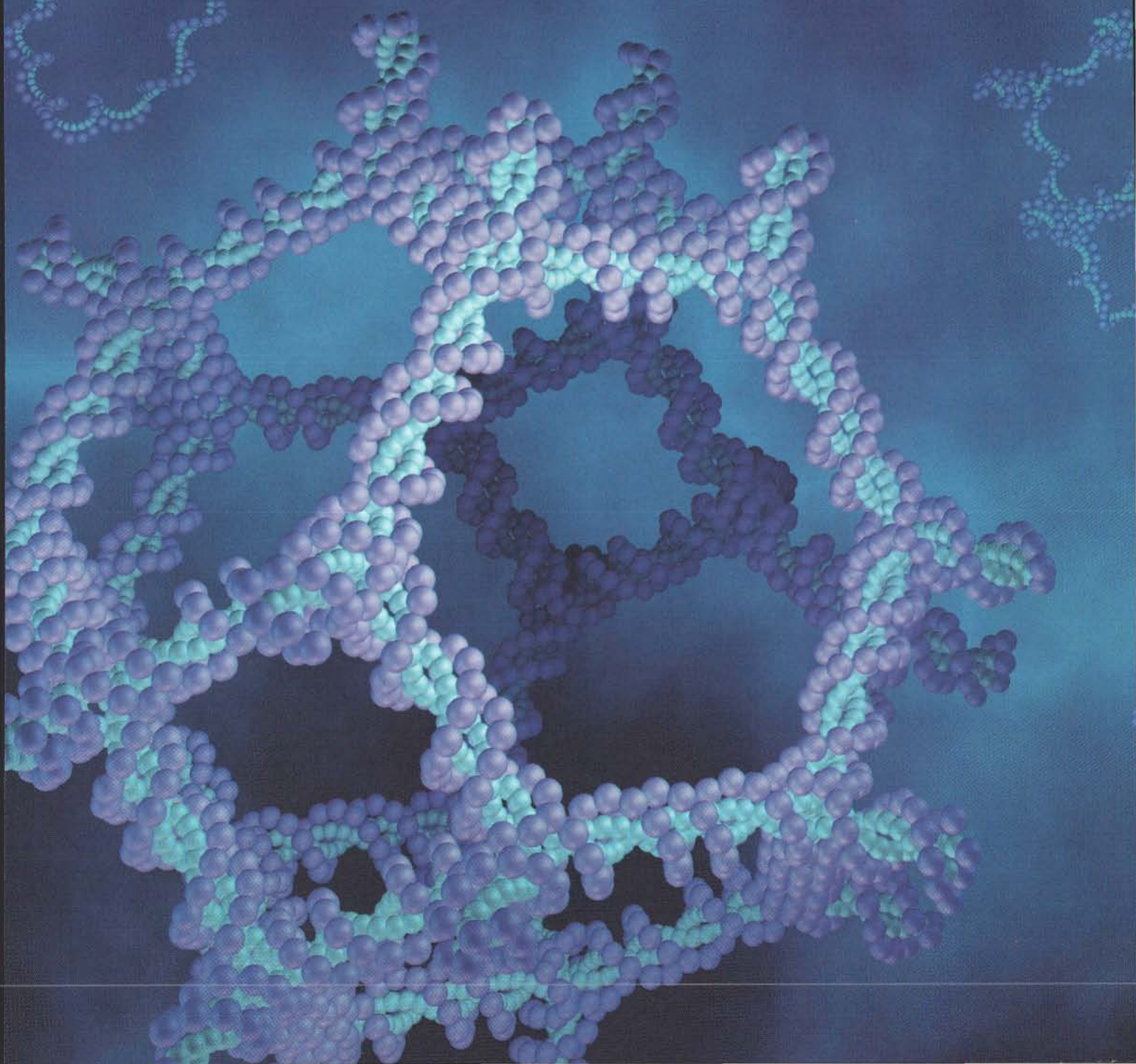
Nanotechnology and the Double Helix



DNA is more than just the secret of life—it is also a versatile component for making nanoscopic structures and devices

By Nadrian C. Seeman

The year 2003 witnessed the 50th anniversary of the discovery of DNA's double-helix structure by James D. Watson and Francis H. Crick. Their discovery reduced genetics to chemistry and laid the foundations for the next half a century of biology. Today thousands of researchers are hard at work deciphering the myriad ways that genes control the development and functioning of organisms. All those genes are written in the medium that is DNA.

Yet this extraordinary molecule has other uses in addition to those of biochemistry. By employing the techniques of modern biotechnology, we can make long DNA molecules with a sequence of building blocks chosen at will. That ability opens the door to new paths not taken by nature when life evolved. In 1994, for example, Leonard M. Adleman of the University of Southern California demonstrated how DNA can be used as a computational device [see "Computing with DNA," by Leonard M. Adleman; SCIENTIFIC AMERICAN, August 1998]. In this article I will discuss another nonbiological use of DNA: the building of structures and devices whose essential elements and mechanisms range from around one to 100 nanometers in size—in a word, nanotechnology.

Such structures have many potential applications. Regular lattices made of DNA could hold copies of large biological molecules in an ordered array for x-ray crystallography to determine their structure, an important step in the "rational" design of drugs. Alternatively, the lattices could serve as scaffolding for nanoelectronic components, either as a working device or as a step in the manufacture of a device. Materials could be constructed—either made of the DNA or made by it—with structures precisely designed at the molecular level. DNA machines with moving parts could be employed as nanomechanical sensors, switches and tweezers as well as for more elaborate robotic functions.

Branched DNA

THE NANOSCALE is the scale of molecules. A typical bond between two atoms is about 0.15 nanometer long. (A nanometer is a billionth of a meter.) The helix of DNA has a diameter of about two nanometers, and it twists full circle once every 3.5 nanometers or so, a distance of about 10 base pairs, which form the "rungs" of DNA's ladder [*see upper illustration on page 37*]. A short piece of DNA has highly specific interactions with other chemicals, depending on its sequence of base pairs. One can imagine using such pieces to recognize particular molecules or to control the composition of a material by acting as a catalyst. And for many years biologists have used DNA for its recognition properties, especially exploiting the "sticky ends" in genetic engineering. A sticky end occurs when one strand of the helix extends for several

KEN EWARD BioGrafx (*strands, left*); ALICE Y. CHEN (*helix, right*)

DNA STRANDS SELF-ASSEMBLE into a complicated structure when their base sequences are designed to pair up with specific partners. Here a stick model of a truncated octahedron, which has six square faces and eight hexagonal faces, has formed. The edges are about 20 nanometers long. A short "hairpin" of DNA sticks out from each corner. The hairpins could be modified to link truncated octahedra together to form a regular three-dimensional scaffold.

unpaired bases beyond the other [*see lower illustration on opposite page*]. The stickiness is the propensity of the overhanging piece to bond with a matching strand that has the complementary bases in the corresponding order—the base adenine on one strand pairs with thymine on the opposite strand, and cytosine binds with guanine. [For another application using the stickiness of DNA, see "The Magic of Microarrays," by Stephen H. Friend and Roland B. Stoughton; SCIENTIFIC AMERICAN, February 2002.]

At first sight, it does not appear that DNA can lead to interesting structures. Naturally occurring DNA forms a linear chain, like a long piece of twine, so that all one can envision making from it is lines or circles, perhaps snarled up or knotted in one way or another. But a linear chain is not the only form that DNA takes. During certain cellular processes, DNA exists briefly as a branched molecule. This branching occurs when DNA replicates (in preparation for cell division) and during recombination (when genetic material is swapped between matching pairs of chromosomes, as happens when sperm and eggs are produced).

The branches form when the double helix partially unravels into two strands. In replication, each strand is made into a new double helix by the addition of complementary nucleotides all along its length. (A nucleotide is the combination of a base and the corresponding section of the backbone of the helix.) More interesting is the crossover that occurs in recombination, in which two pieces of DNA break and partially unravel and the resulting four strands join up somewhat like the intersection where two highways cross.

In recombining DNA, the branch point occurs where each of the four strands switches from one partner to another. The branch point moves around because of twofold symmetry (like that of the numeral "69") in the base sequences that flank it. This symmetry means that each strand can pair up with either of two other strands. In 1979 I was working with Bruce H. Robinson, now at the University of Washington, to describe the nature of this motion when I recognized that synthetic DNA molecules lacking this symmetry could form branched molecules whose branch points do not move. To design such a junction, one would make four strands of DNA. For each strand, the sequence along half of the strand would match half of a second strand and the remaining half would match half of a third strand [*see lower illustration on opposite page*].

DNA's favorite structure is the conventional double helix identified by Watson and Crick. A quantity called free energy determines which structure is favored. In general, free energy determines whether a chemical reaction proceeds in the forward or reverse direction; it also determines the conformation—the folds and joins—of large molecules such as DNA, RNA and proteins. A chemical system always tends to change toward the state that has the lowest free energy. For two complementary strands of nucleotides, the free energy is minimized when they pair up to form a double helix.

The four strands of our immobile junction can come together and form the maximum amount of conventional DNA double helices only by forming a branched molecule. In general, a branch point is not favored—it increases the free energy of the molecule—but this increase is outweighed by the much greater energy saving in the four arms made of ordinary double-helix DNA. Today it is simple to synthesize such strands and implement this idea of a stable branched DNA molecule, but in 1979 it was state-of-the-art chemistry and I was a crystallographer, not an organic chemist, so mostly I just thought about the system. (It was not until 1982 that I learned how to make DNA.)

STRANDS OF DNA interact in the most programmable way. Their enormous variability provides ample scope for DESIGNING MOLECULES.

Overview/*DNA Nanotech*

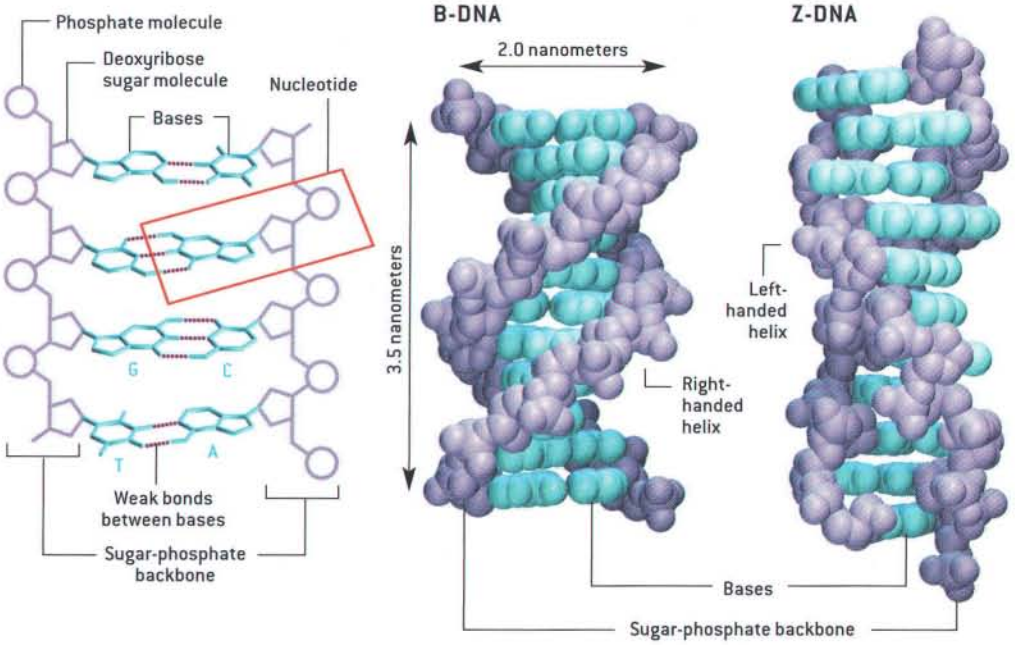
- DNA is an ideal molecule for building nanometer-scale structures. Strands of DNA can be programmed to self-assemble into complex arrangements by producing the strands with the appropriate combinations of complementary bases, which preferentially bond together to form stretches of double helices.
- DNA scaffolds could hold guest molecules in orderly arrays for crystallography. They could also hold molecule-size electronic devices, or be used to build materials with precise molecular configurations.
- Nanometer-scale DNA machines can function by having parts of their structure change from one DNA conformation to another. These movements can be controlled by chemical means or by the use of special DNA strands.

Inspiration from Escher

I FIGURED OUT that it ought to be possible to make branched DNA junctions with many arms, not just four. One day, in the fall of 1980, I went over to the campus pub to think about six-arm junctions. For some reason, I thought about Dutch artist M. C. Escher's woodcut *Depth* [*see illustration on page 38*]. I realized that the center of each fish in that picture was just like an idealized picture of the branch point of a six-arm junction. Six features extend from that center point on the fish: a head and a tail, a top fin and bottom fin, a left fin and a right fin. The fish are organized in the same way as the molecules in a molecular crystal, with regular repeats forward and back, up and down, left and right. It struck me that if I held junctions together using sticky ends, I might be able to organize matter on the nanometer scale in the same way that Escher held his school of fish together using his imagination.

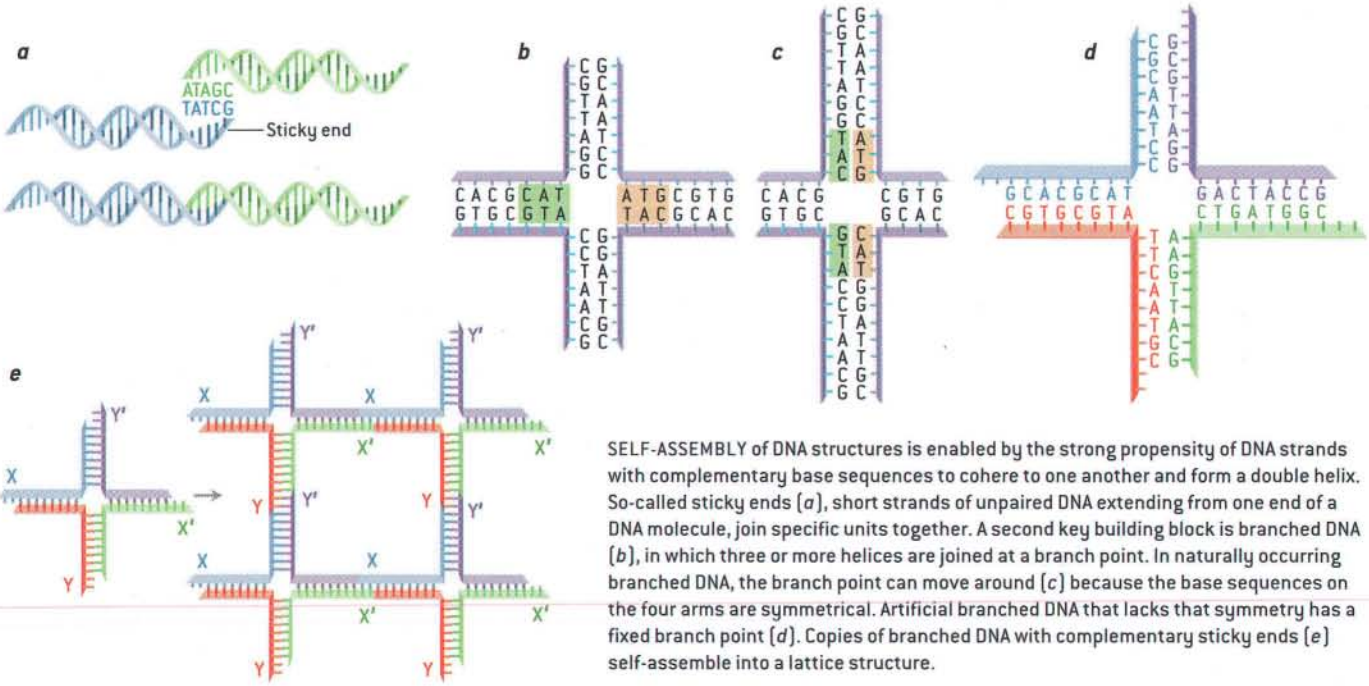
THE STRUCTURE OF DNA

DNA is a nanoscale structure, consisting of a double backbone of phosphate and sugar molecules between which complementary pairs of bases (A and T; C and G) are connected by weak bonds (*left*). DNA's most common conformation is B-DNA (*center*), which twists in a right-handed double helix about two nanometers in diameter. One full turn of the helix is about 3.5 nanometers, or 10 to 10.5 base pairs long. In special circumstances DNA can form a left-handed double helix called Z-DNA (*right*).



We have several good reasons for wanting to build such structures. First, we are aiming to fabricate macroscopic pieces of matter made of designed molecules joined together in a structure that is controlled with nanoscopic precision. This procedure could result in materials having novel properties or novel combinations of properties. For example, materials with designed optical properties, such as photonic crystals, could be made by constructing precisely defined arrays with specific repeat distances [see "Photonic Crystals: Semiconductors of Light," by Eli Yablonovitch; SCIENTIFIC AMERICAN, December 2001].

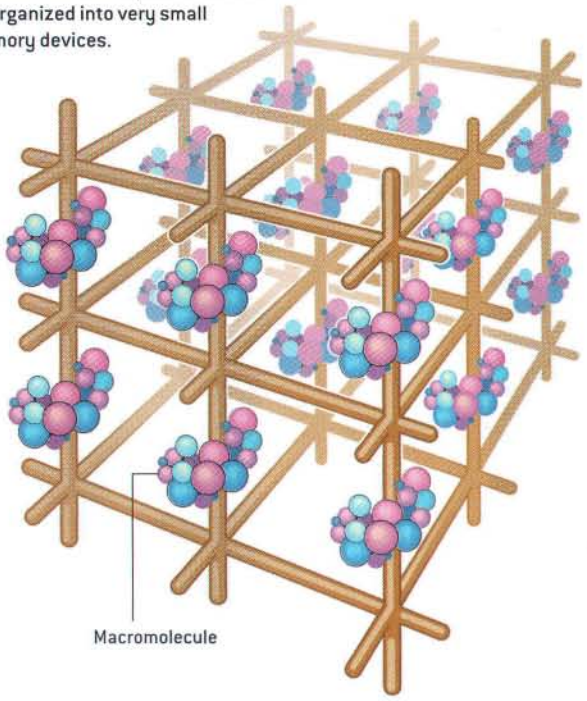
Another goal is to use DNA as scaffolding to hold other molecules in arrays, including those that do not form a regular crystalline structure on their own. In this way, one could make crystals for use in crystallography experiments by making DNA cages that contain large biological molecules such as proteins within them [*see right illustration on next page*]. Such cages



SELF-ASSEMBLY of DNA structures is enabled by the strong propensity of DNA strands with complementary base sequences to cohere to one another and form a double helix. So-called sticky ends (*a*), short strands of unpaired DNA extending from one end of a DNA molecule, join specific units together. A second key building block is branched DNA (*b*), in which three or more helices are joined at a branch point. In naturally occurring branched DNA, the branch point can move around (*c*) because the base sequences on the four arms are symmetrical. Artificial branched DNA that lacks that symmetry has a fixed branch point (*d*). Copies of branched DNA with complementary sticky ends (*e*) self-assemble into a lattice structure.

KEN EWARD *BioGrafx* (*top*); ALICE Y. CHEN (*bottom*)

ESCHER'S WOODCUT *DEPTH* (*left*) inspired the author to consider an array of six-arm junctions connected together to form a three-dimensional molecular crystal (*below*). The center of each fish is just like the branch point of a six-arm junction. Instead of arms, six features extend from that center point: a head and a tail, a top and bottom fin, and a left and right fin. Molecular scaffolding could hold other molecules in regular arrays. For example, DNA cages containing oriented biological macromolecules as guests could be used in crystallography experiments. In a similar fashion, nanoelectronic components could be organized into very small memory devices.



would enable crystallographers to determine the three-dimensional structures of the enclosed molecules—a key procedure in the rational design of drugs that mesh precisely with specific parts of a targeted molecule. (This crystallographic application is the one that most strongly motivates my interest in this field.) Currently many of the receptor molecules that could be excellent drug targets do not lend themselves to conventional crystallography. In a similar fashion, one could organize nanoelectronic components into very small memory devices, as Robinson and I suggested in 1987. My group has not used DNA as scaffolding yet, but we have had many other successes that are steps on the way to achieving this goal.

Why use DNA for these purposes? The chief reason is that strands of DNA interact in the most programmable and predictable way. A sticky end that is N bases long has one of 4^N possible sequences of bases. This enormous variability and the propensity of the end to bond to only a closely matching sequence provide ample scope for designing molecules that consist of a large number of DNA strands joined to one another in a completely specified manner. Furthermore, we know that two sticky ends form the classic helical DNA structure when they cohere, and these helical stretches of DNA are relatively stiff. Thus, we know not only which strands link to which other strands but also the detailed shape of the joined segments. We do not have such specific information for proteins or antibodies, which are other candidates for working elements. Those also have tremendous variability, but determining what shape a protein will take and how two proteins or antibodies will join together are laborious problems that would have to be solved anew for each example.

Another reason for working with DNA is the simplicity of its synthesis with the tools of the biotechnology industry. We can manipulate DNA with many enzymes, such as restriction enzymes (which cleave DNA at particular sites) or ligases (which catalyze the joining of two molecules by covalent bonds—sturdy chemical bonds that involve the sharing of pairs of electrons between atoms). These tools can be used to make and manipulate conventional DNA, as well as exotic derivatives, in which different bases from the usual four are incorporated or in which

THE AUTHOR

NADRIAN C. ("NED") SEEMAN trained in crystallography, but his frustrations with a macromolecular crystallization experiment led him to the idea that DNA junctions could be used in a new approach to crystallization. Ever since then, he has been trying to implement this concept and its spin-offs. For the past 16 years, Seeman has worked in the department of chemistry at New York University. When told in the mid-1980s that what he was doing was nanotechnology, his response was similar to that of M. Jourdain, the title character of Molière's *Bourgeois Gentilhomme*, who was delighted to discover that he had been speaking prose all his life.

additional molecules are attached on the outside of the DNA's backbone (the sides of the DNA ladder). Medical researchers hoping to use nucleic acids (DNA and RNA) for therapy have made many such variants. DNA is extremely well suited to making such derivatives because every nucleotide along the helix has sites where molecules can be attached.

Finally, as we will see below, DNA can be induced to form structures different from the standard double helix. We can build nanomechanical devices whose parts move—such as closing tweezers or a rotating shaft—when there is a transition from one DNA structure to another. One drawback is that DNA objects must be constructed in an aqueous solution. It is no problem, however, to dry the resulting structures (on mica, for instance) as we do to make microscopic images of our results.

Stick Models

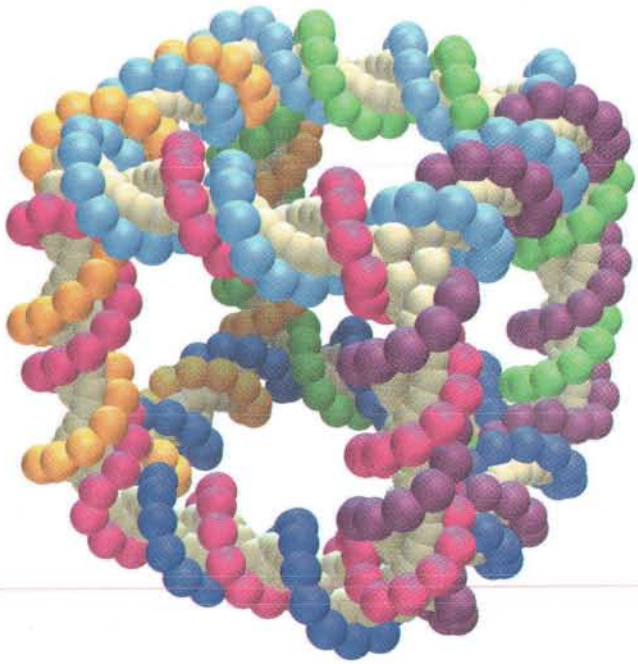
THE FIRST STEP in any new scientific research program is to establish the basic feasibility of the project. In 1991 Junghuei Chen, now at the University of Delaware, and I did this by building a DNA molecule shaped like a cube formed from sticks [*see illustration below*]. Each edge of the cube is a stretch of double-helical DNA; each corner is a three-arm junction. Each corner is connected to three other corners; it is said that the cube's connectivity is three. Genetic engineers had made many linear DNA constructs, but this was the first DNA molecule with connectivity greater than two. The cube self-assembles from pieces of DNA designed to adhere to one another, but the ends of each piece do not join up. Ligases can connect these free ends, resulting in six closed loops, one for each face of the cube. Because of the helical nature of DNA, each of these loops is twisted around the loops that flank it, so the cube cannot come apart, even if all the bonds joining the base pairs together were somehow broken.

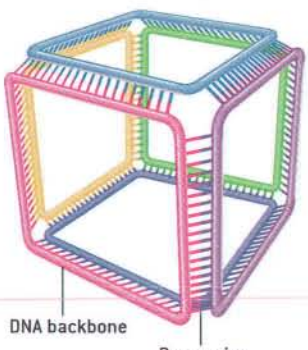
Yuwen Zhang, now at Baxter Healthcare, and I built another shape called a truncated octahedron, which is similar to but more complicated than a cube [*see illustration on page 34*]. Although three-arm junctions would have sufficed to make individual truncated octahedra, instead we built them using four-arm junctions. We intended that the extra arm sticking out at each corner could be used to connect truncated octahedra together in a larger structure, but in the end we did not continue in this direction. We had created only a very tiny quantity of truncated octahedra—enough to characterize their structure but too few to attempt to join them together—and even that minute sample had taken us to the limits of what we could do without overhauling our procedures (for example, by robotizing repetitive steps). Instead we turned to simpler components.

Another reason for changing direction was that along the way we realized that the stick polyhedra we had built were not rigid. DNA is a stiff molecule: a stretch of DNA that is two or three turns long (the lengths we use for the polyhedra edges) can wiggle around its helix's axis no more than a piece of cooked spaghetti two or three millimeters long can wiggle around its central axis. That inflexibility ensured that the edges of our stick figures were rigid, but we learned that the angles at each corner were quite variable. The polyhedra we had built were rather like structures made of toothpicks stuck into blobs of marshmallow at the corners. Such structures might have uses, but building a regular lattice is not one of them. It is much easier to self-assemble an orderly, crystallike piece of matter from bricklike components than from marshmallows.

THE POLYHEDRA we had built were rather like structures made of toothpicks stuck into BLOBS OF MARSHMALLOW at the corners.

To solve this problem, my group examined another branched motif found in biological recombination systems, the DNA double-crossover (DX) molecule. The DX molecule consists of two double helices aligned side by side, with strands crossing be-



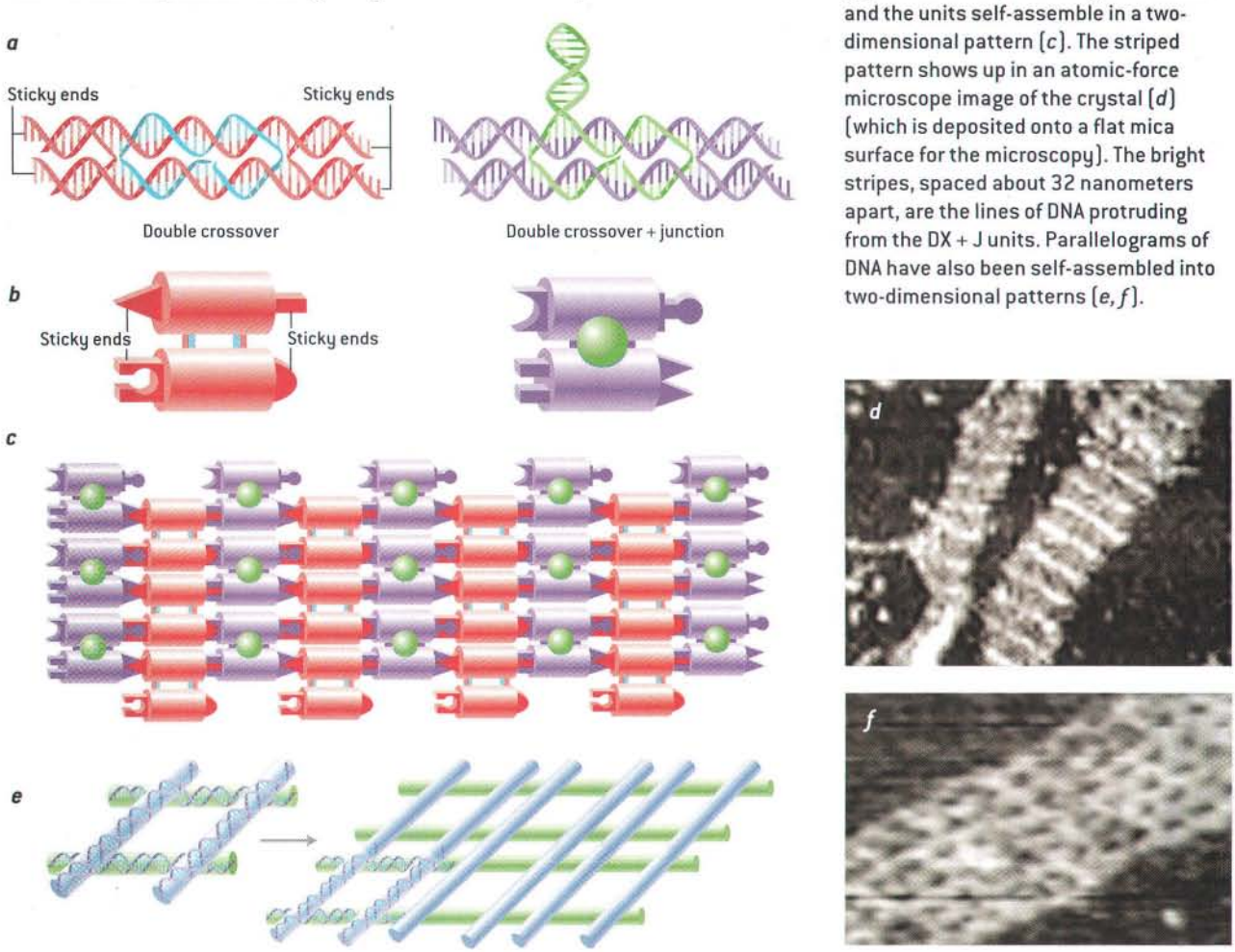


STICK CUBE (*far right*) made out of six loops of DNA demonstrated that three-dimensional structures can be built. The backbone of each DNA strand is depicted as colored spheres (a different color for each strand) and the bases as white spheres. Each edge of the cube comprises 20 nucleotide pairs, or about two complete turns of the double helix. Each corner is a three-arm junction. Simplified schematic (*near right*) depicts how the DNA strands are connected but omits the helical twists.

ALICE Y. CHEN (*left*); KEN EWARD *BioGrafx* (*right*)

STIFF DNA ARRAYS

Two-dimensional crystals can be made out of stiff bricks of DNA. The bricks (*a*) are double-crossover (DX) and double-crossover-plus-junction (DX + J) units, which cannot flop around at their joining points the way that multiarm junctions can. Each brick has four distinct sticky ends for joining bricks together. The extended green strand of the DX + J unit sticks out of the plane. Each unit is about 4 by 16 nanometers in size. For simplicity, the DX and DX + J units are shown schematically, with geometric shapes at their ends representing the sticky ends (*b*). In a solution, the sticky ends cohere and the units self-assemble in a two-dimensional pattern (*c*). The striped pattern shows up in an atomic-force microscope image of the crystal (*d*) (which is deposited onto a flat mica surface for the microscopy). The bright stripes, spaced about 32 nanometers apart, are the lines of DNA protruding from the DX + J units. Parallelograms of DNA have also been self-assembled into two-dimensional patterns (*e*, *f*).



tween the helices, yoking them together [*see box above*]. We characterized this molecule and established that it is stiff. We also demonstrated that a DX molecule containing another small double helical region (called a DX + J molecule) is very stiff. This additional double helical region creates a bump on the top of the DX molecule, which serves as a marker—a nanotech equivalent of a dab of paint.

In collaboration with Erik Winfree of the California Institute of Technology, Furong Liu and Lisa A. Wenzler of my group at New York University used combinations of DX and DX + J molecules as tiles to make two-dimensional crystals with defined patterns. The tiles are joined together by sticky ends on each helix. One arrangement, with columns of DX tiles alternating with columns of DX + J tiles, produces a pattern of stripes separated by about 32 nanometers. We deposited the arrays on a flat mica surface and examined them with an atomic-force microscope to confirm that the structure had the correct dimensions. We established that the pattern was not accidental by making a second crystal with modified tiles that link together with three DX columns for each DX + J column, to produce stripes with double the separation.

Recently John H. Reif's group at Duke University demonstrated "DNA bar codes" made using such patterns. In these tilings, the positions of stripes were programmed to occur in a pattern representing the number "01101" (with molecules analogous to our DX and DX + J serving as 0 and 1, respectively). The pattern was programmed using an input DNA strand whose sequence encoded the 01101 pattern. The analogues of the DX and DX + J bricks self-assembled on the sections of the DNA strand corresponding to 0 and 1, respectively. Many such

ALICE Y. CHEN (*illustrations*); NADRIAN C. SEEMAN (*micrographs*)

five-brick sequences then joined up in parallel, generating the 01101 pattern of stripes. The stripes were about 15 nanometers apart. By examining the stripes with an atomic-force microscope, one is effectively using the bar code to read out the data that were encoded on the input DNA strand. This visual means of reading out the DNA sequence could greatly speed up the readout stage of DNA-based computing and might also be used for mapping mutations.

Chengde Mao, now at Purdue University, and I have made two-dimensional patterns from DNA parallelograms similar to our stick polyhedra. Copies of this unit can be joined to form a crystal that extends like a waffle in two dimensions. One can tune the sizes of the cavities in the array by changing the dimensions of the parallelograms. Although individual branched junctions are floppy, arranging four of them at the corners of a parallelogram results in a well-behaved unit in a parallelogram array.

A CRUCIAL GOAL for nanotechnology based on DNA is to extend the successes in two dimensions TO THREE DIMENSIONS.

Nanomachines

CENTRAL TO NANOTECHNOLOGY are molecular-scale machines. DNA has proved to be very useful for constructing these machines. We have built several devices from DNA, but here I will focus on two that have well-defined structures. In both cases, the mechanism is based on a structural transition of DNA molecules—a change from one conformation (such as the usual double helix) to another.

Conventional DNA is a right-handed helix. Imagine walking up a spiral staircase with your left hand on the inner banister and your right hand on the outer one. Such a staircase is a right-handed helix. Conventional right-handed DNA is called B-DNA and is the most energetically favored structure in typical aqueous conditions.

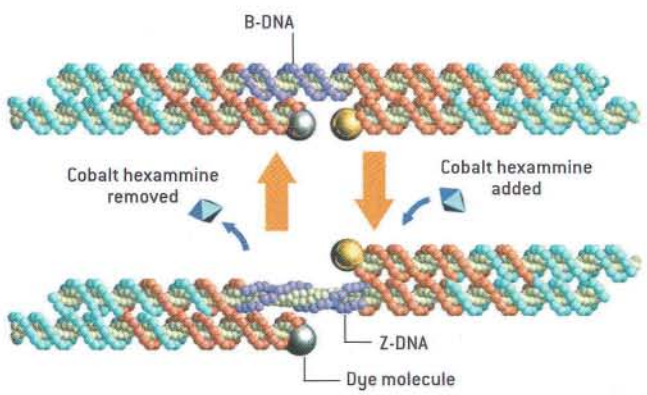
Double-helical DNA can also assume a number of different structures depending on its base sequence and the chemical species present in the solution in which it is immersed. One is Z-DNA, whose structure was first characterized in 1979 by Alexander Rich and his colleagues at the Massachusetts Institute of Technology [*see upper illustration on page 37*]. Z-DNA is a left-handed DNA structure.

To make Z-DNA typically requires a stretch of alternating cytosine and guanine bases. The DNA backbone includes negatively charged phosphate groups, and these come close together in the Z-DNA structure. This formation is favored only if the charges of the phosphates can be screened from one another by an aqueous environment containing either a high concentration of salt or a special "effector" species, such as cobalt hexammine, $Co(NH_3)_6^{+++}$, that does the same job at a much lower concentration. The cytosine-guanine sequence requirement lets us control *where* on a DNA molecule the B-Z transition takes place (and hence *what* our machine does), and the environmental requirement lets us control *when* the transition (and hence the machine action) occurs.

My N.Y.U. colleagues Weiqiong Sun and Zhiyong Shen, Mao and I built a device consisting of two DX molecules connected by a shaft of double-helical DNA [*see illustration below*]. In the middle of the shaft is a sequence of 20 pairs that can adopt the Z-structure in the appropriate conditions. In ordinary conditions, every part of the device will form B-DNA and the two DX molecules will both be on the same side of the shaft's axis. When cobalt hexammine is added to the solution, the central part of the shaft converts to Z-DNA and one DX molecule rotates about 3.5 turns relative to the other; the odd half-turn means that they are now on opposite sides of the shaft's axis. Removal of the cobalt hexammine reverts the device back to its original structure. We demonstrated that the motion was taking place by using spectroscopy involving two colored dyes attached to the DX molecules.

This B-Z device is quite robust, but it suffers from a flaw. Were a bunch of different B-Z devices incorporated into a larger superstructure (for example, one of the two-dimensional lattices discussed earlier), the entire structure would have only two states: every machine in the B state or every one in the Z state. To control a collection of machines individually requires devices with independent triggers. With DNA, of course, there is a natural way to do this, by using DNA strands as the triggers and having a different base sequence trigger each machine.

To implement this scheme, Hao Yan, now at Duke, Xiaoping Zhang of New York University, Shen and I devised a system that changes shape when different strands bind to it. The



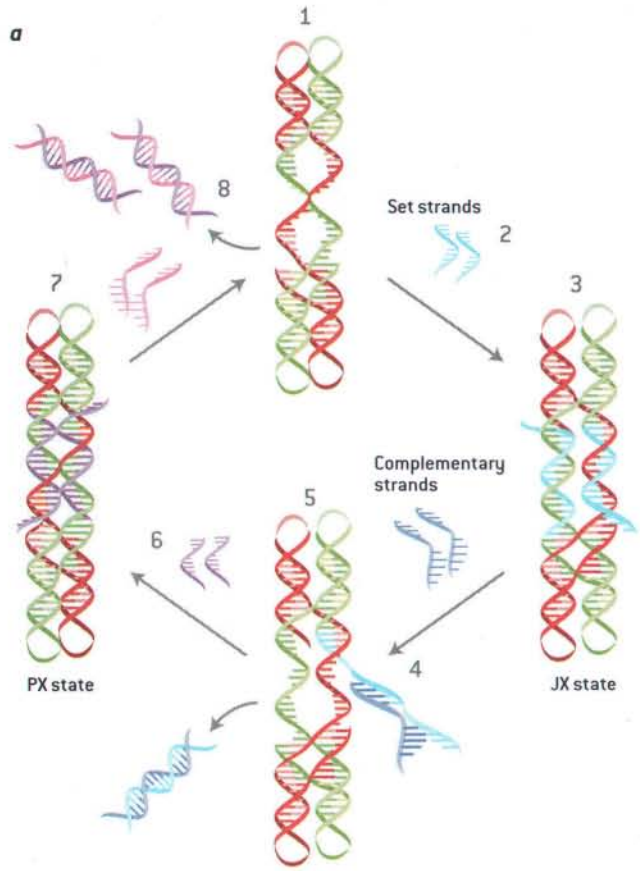
NANOMECHANICAL B-Z DEVICE that demonstrates controlled movement is made of two DX units (*blue* and *orange*) joined by a shaft of 20 base pairs (*purple*). Two colored dye molecules (*silver* and *gold spheres*) highlight the positions of the DX molecules. In the B state (*top*), the shaft is ordinary right-handed B-DNA and both DX molecules are on the same side. When cobalt hexammine is added to the solution, the shaft converts to left-handed Z-DNA [*see upper illustration on page 37*] and the DX units rotate through 3.5 turns relative to each other, ending up on opposite sides of the shaft.

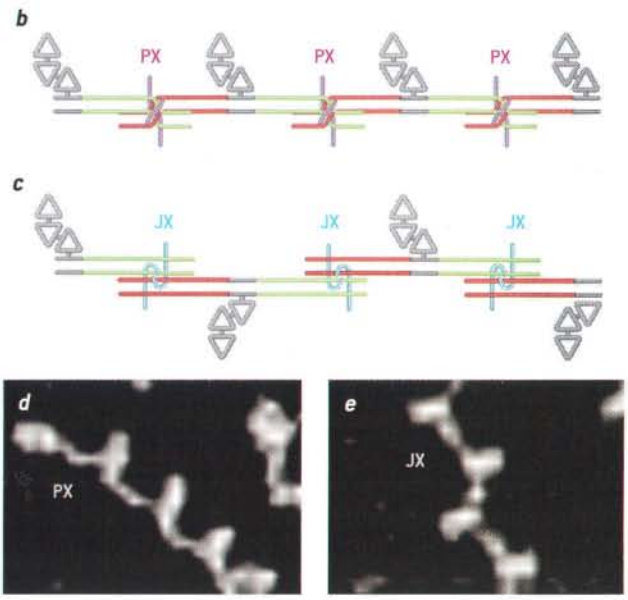
KEN EWARD *BioGraf/x*

USING DNA AS A TRIGGER

Individually controllable DNA device is switched between two states (*a, steps 1–8*) by the addition and removal of specific stretches of DNA called set strands. The naked device consists of four double helices connected in the middle by two unpaired DNA strands (*1*). When the light-blue set strands are added (*2*), they bind to the unpaired strands in a way that forces the device into the "doubly juxtaposed" (JX) state (*3*). In this state, the red and green helices are on the same side, top and bottom. The light-blue strands are stripped away when complementary strands are added (*4*), leaving the device naked again (*5*). Now the purple set strands are added (*6*), which bind in a different way, forcing the device into the so-called paranemic crossover (PX) state (*7*). This rotates the lower part of the device, putting the red and green helices on the opposite sides. The machine's cycle can continue with the stripping away of the purple strands (*8*) and the reintroduction of the light-blue strands.

The functioning of this device was verified by connecting copies of it in a chain, with large trapezoid-shaped pieces of DNA attached as markers. When the devices are in the PX state (*b, below*), all the trapezoids are on the same side. When all the devices are in the JX state (*c*), the trapezoids alternate sides. Atomic-force microscopy revealed precisely this pattern of behavior (*d, e*).





system consists of two parallel DNA double helices that each reduce to a single strand in a central crossover region. The crossover region can assume two different states according to which particular strands have been added to the solution to bind to the single-strand sections [*see box above*]. The two states of the device are called PX ("paranemic crossover") and JX ("juxtaposed"). When the device is in the PX state, the two helices on one side of the central junction are rotated about a half-turn from their positions in the JX state.

Adding a particular pair of strands (called set strands) to the solution puts the device in the JX state by binding to the central region without crossing over. To change to the PX state, we must first remove these set strands. In 2000 Bernard Yurke and his colleagues at Lucent Technologies showed that a strand can be extracted from DNA by binding the strand's full complement to it. To implement this process, our set strands have short ends that remain unpaired with the machine. When we add a full complementary strand to the solution, it begins by joining to the unpaired extension and then strips off the rest of the set strand from the device.

With the first set strands removed from the frame, we can then add different set strands, which bind to the central region and cross over there. That binding turns the two double helices and puts the device in the PX state. The process can be reversed by removing the second set strands and adding back the first ones. In this way, the double helices can be turned back and forth at will. A number of different PX-JX devices can be operated independently by adding and removing set strands designed for their individual binding regions.

We used atomic-force microscopy to verify how our device moved. We made a long chain of these devices and connected a large trapezoid-shape DNA unit to one side of each device.

ALICE Y. CHEN [*illustrations*]; NADRIAN C. SEEMAN [*micrographs*]

When all the devices are in the PX state, the trapezoids lie on the same side of the chain. When all are in the JX state, the trapezoids alternate sides, in a zigzag pattern.

In 2000 Yurke and his colleagues demonstrated nanoscopic "tweezers" made of three strands of DNA. Set strands, which Yurke calls fuel strands, opened and closed the tweezers. Other researchers have used similar methods to switch on the activity of ribozymes—enzymes made of RNA. In 1998 Michael P. Robinson and Andrew D. Ellington of the University of Texas at Austin demonstrated a 10,000-fold enhancement of a ribozyme's activity by the addition of an appropriate set strand, which bound to the ribozyme, changing its conformation.

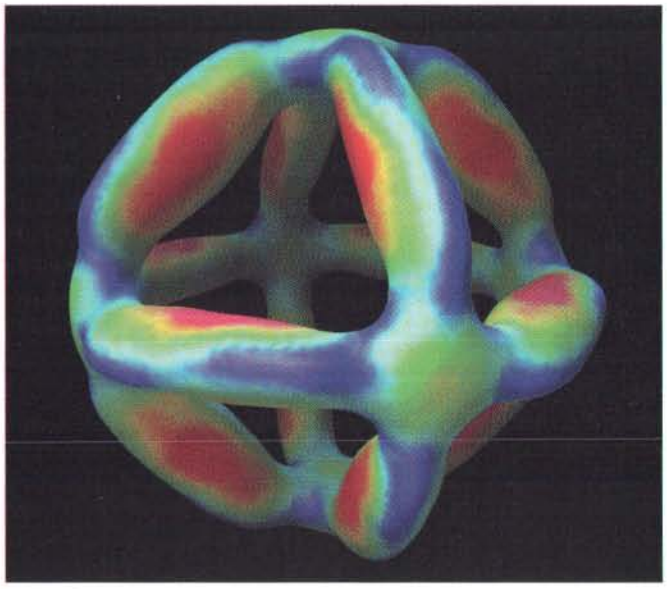
The Future

A CRUCIAL GOAL for nanotechnology based on DNA is to extend the successes in two dimensions to three dimensions. When that has been accomplished, we will have demonstrated the ability to design solid materials by specifying a series of DNA sequences and then combining them. If the systems are highly ordered, then the crystallographic experiments involving molecules held within a regularly repeating framework mentioned earlier will be feasible.

Another goal is to incorporate DNA devices within the frameworks. This accomplishment would be the first step toward nanorobotics involving complex motions and a diversity of structural states, which would enable us to build chemical assembly lines. Using devices similar to the ones described here, we could assemble new materials with high precision. As a prototype, James W. Canary and Philip S. Lukeman of N.Y.U., Lei Zhu, now at the University of Texas at Austin, and I recently assembled a small piece of nylon on a nucleic acid backbone. Someday we expect to be able to make new polymers with specific properties and topologies (such as windings of their backbones).

Achieving these goals primarily entails the use of DNA as a programmable component, but neither crystallography nor nanoelectronics can rely on DNA alone. For instance, nanoelectronic components, such as metallic nanoparticles or carbon nanotubes, will have to be combined with DNA molecules in systems and liquid solutions that are compatible with both the DNA and the other components. Given the diverse chemical nature of these molecules, achieving this will not be simple. In addition, even if the nanoelectronics can be constructed by DNA self-assembly, the nanomachines ultimately need to interact with the macroscopic world in a manner that is more sophisticated than the addition and removal of set strands from a solution. This challenge is likely to be formidable.

A nanotechnological dream machine is one that can replicate. Unlike linear DNA, however, branched DNA does not lend itself readily to self-replication. Yet late last year William M. Shih, Joel D. Quispe and Gerald F. Joyce of the Scripps Research Institute in La Jolla, Calif., took an exciting first step toward self-replicating DNA objects. They built an octahedron from one long strand of DNA (about 1,700 bases), using five short "helper" strands to complete the assembly [*see illustration below*]. Each edge of the octahedron is made of two interlinked DNA double helices—a series of DX and PX molecules. The edges were each about 14 nanometers long, or about four turns of a double helix. A folded octahedron cannot reproduce, but in the unfolded state, the long strand is readily cloned millions of times by a standard biotechnology process called PCR (polymerase chain reaction). It is still a far cry from the replication achieved by every living organism, but by the time the Watson-Crick centenary comes around, we should have DNA-based machines that do as well. SA



DNA OCTAHEDRON shown here was built out of one long strand of DNA and five short "helper" strands. Each strut consists of two parallel, interlinked double helices. The image was reconstructed by combining data from cryo-electron microscope images of more than 600 octahedra. The colors represent relative electron density: red high and blue low.

MIKE PIQUE *Scripps Research Institute*

MORE TO EXPLORE

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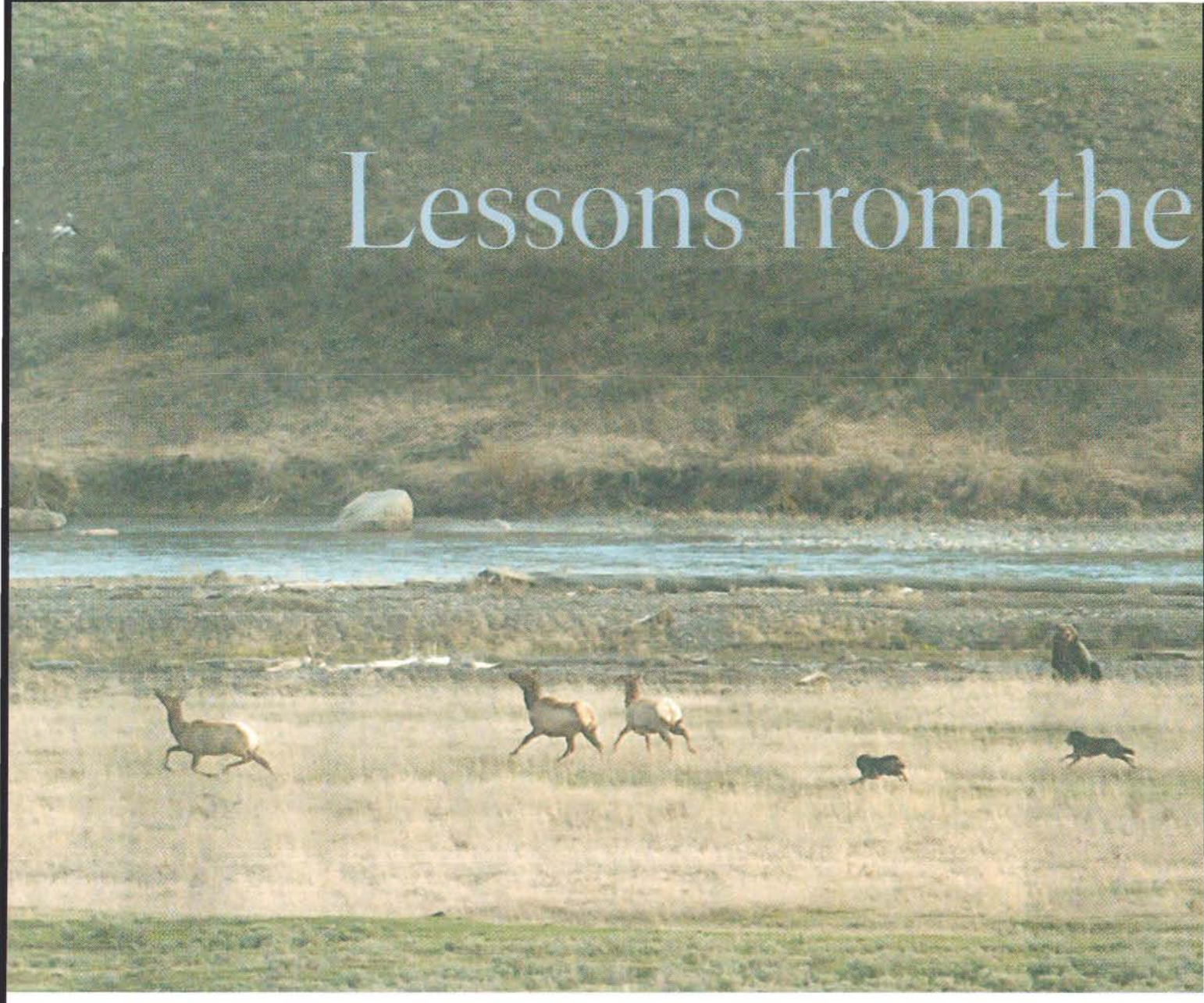
Nadrian C. Seeman's laboratory Web site: **http://seemanlab4.chem.nyu.edu/**

Lessons from the

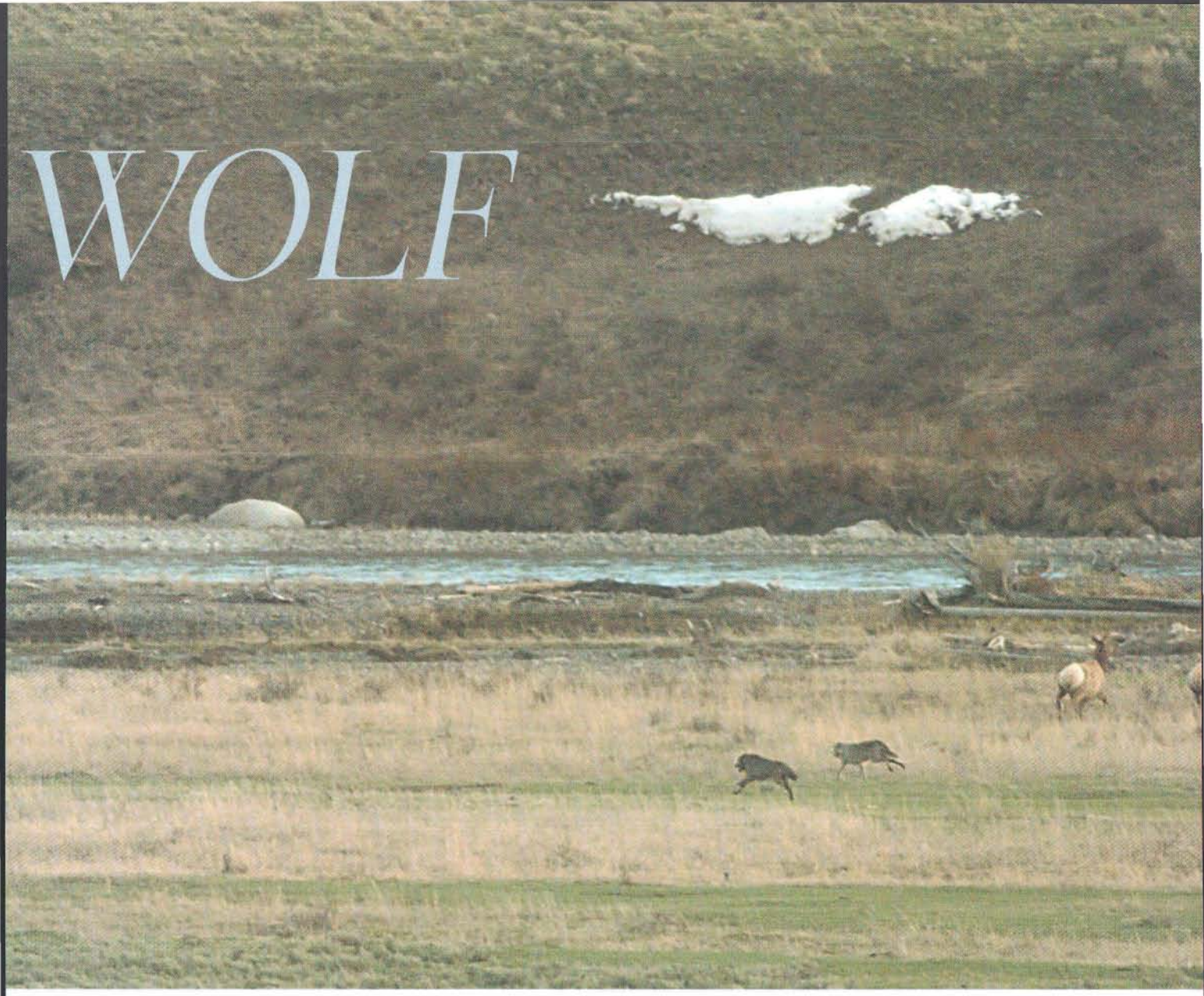


Bringing the top predator back to Yellowstone has triggered a cascade of unanticipated changes in the park's ecosystem

Several scrawny cottonwood trees do not usually generate much excitement in the world of ecology. But on a wind-whipped August afternoon in Yellowstone National Park's Lamar Valley, William J. Ripple, a professor of botany at Oregon State University, stands next to a 12-foot-high cottonwood tree and is quietly ecstatic. "You can see the terminal bud scars," the bespectacled Ripple says, bending the limber tree over to show lines that mark a year's growth of a foot or more on the broom-handle-size trunk. "You can see that elk haven't browsed it this year, didn't browse it last year and, in fact, haven't browsed it since 1998."

Ripple gestures at the sprawling mountain valley around us and points out that although numerous other cottonwoods dot the landscape, this knot of saplings comprises the only young ones—the rest of this part of the Lamar is a geriatric ward for trees. The stately specimens that grow in the valley bottom are 70 to 100 years old,

WOLF



By Jim Robbins

EARLY SPRING in the Lamar River Valley: several wolves chase elk while an interested grizzly bear awaits the outcome. Grizzlies can drive wolves off a kill; more often they scavenge after the wolves have eaten their fill.

and not a newcomer is in sight to take their place. On the hillside, aspen trees present a similar picture. Groves of elderly aspen tremble in the wind, but no sprouts push up in the understory.

These trees could have died out entirely, some experts believe, if wolves hadn't shown up in Yellowstone. And therein lies a fascinating tale of how ecosystems work, and how making one change can produce all sorts of surprises.

In the dead of winter in 1995 the National Park Service and the U.S. Fish and Wildlife Service brought 14 wolves into Yellowstone by truck and sleigh. Gray wolves (*Canis lupus*) from Canada, these were the first to call Yellowstone home since the creatures were hunted out of existence there early in the 20th century. A year later 17 more Canadian wolves were added.

Biologists hoped that the reintroduction would return the mix of animals

DIANE HARGREAVES

YOUNG WOLF tests the air. By midsummer, pups are mature enough to leave the den and join their parents in socializing with other wolves.

JIM McGRAW *WildEye Images*

to its more natural state. They expected, for instance, that the wolves would cull many of the elk that lived in the park. When the wolves—once the region's top predator—were gone, the elk population had burgeoned. And the new generation of *Canis* behaved as predicted. Sixteen packs of wolves, each composed of about 10 animals, now roam the park, and each pack kills an average of one elk a day. The elk population, which had swollen to 20,000 by the 1990s, is now less than 10,000.

The wolf introduction has had numerous unexpected effects as well. The animals' impact on the flora and fauna in the park has been profound. Indeed, the breadth of change has been so far-reaching that researchers from around the country have come to study the alterations. "Wolves are shaping what you see here," says Douglas W. Smith, leader of the Yellowstone Wolf Project. "In 30 years, when you drive through the park, it will look very different."

The Ecology of Fear

RIPPLE, FOR ONE, is hoping for more trees. "I like aspen trees," he remarks over coffee in a cozy log restaurant near a cabin just outside Yellowstone where he stays during field research. "I am passionate about them." Among other things, he explains, they are biodiversity hot spots in the West, home to a variety of songbirds. When he heard in 1997 that aspen trees were on the decline in Yellowstone and no one knew why, he was drawn to the park to try to solve the mystery.

Ripple points to some black-and-white photographs taken of the same spot in the Lamar Valley more than 50 years apart. "You can see that young aspen and willow were abundant in the early 1900s. By the 1930s the trees had stopped regenerating, and there are no young ones.

"I had a lightbulb," he continues. He took core samples from 98 aspen trees and discovered that only two had begun to grow after the 1920s—around the time the last substantial populations of wolves were killed or driven off. And these two were in places that elk would be hesitant to frequent for fear of being attacked by predators. Ripple found big trees and tiny trees but nothing in between, because nothing new grew from the 1930s to the 1990s. It was the first concrete evidence of a "wolf effect."

The wolf-effect theory holds that wolves kept elk numbers at a level that prevented them from gobbling up every tree or willow that poked its head aboveground. When the wolves were extirpated in the park as a menace, elk numbers

Overview/*Return of the Wolves*

- The National Park Service and the U.S. Fish and Wildlife Service "repatriated" wolves to Yellowstone National Park in 1995 and 1996.
- Many observers believe the wolves have reduced the elk population of the park (now down by about half), which has in turn spurred regrowth of vegetation.
- Lusher vegetation has lured the beaver back, and their dams have created ponds, encouraging still more new vegetation.
- Wolves have also wrought changes in the lives of the park's other animals: coyotes, grizzlies, red foxes, ravens, even songbirds.

soared, and the hordes consumed the vegetation, denuding the Lamar Valley and driving out many other species. Without young trees on the range, beavers, for example, had little or no food, and indeed they had been absent since at least the 1950s. Without beaver dams and the ponds they create, fewer succulents could survive, and these plants are a critical food for grizzly bears when they emerge from hibernation.

After the wolves' reintroduction in 1995 and 1996, they began to increase their numbers fairly rapidly, and researchers began to see not only a drop in the population of elk but a change in elk behavior. The tall, elegant mahogany-colored animals spent less time in river bottoms and more time in places where they could keep an eye out for predatory wolves. If the wolf-effect hypothesis is correct, and wolves are greatly reducing elk numbers, the vegetation should be coming back for the first time in seven decades.

Hiking along the purling Lamar River, not far from a den of one of the wolf packs, Ripple walks by a small rise and parts a dense green curtain of booth willows to make a point. There on the ground lie the bleached skull, ribs and spine of an elk. And all around, the willows are much taller than Ripple, some more than three meters high. Ripple and his colleague Robert L. Beschta, a forester at Oregon State University, have indeed found trees and willows rebounding in Yellowstone as wolf numbers have climbed—but that is only part of the change occurring in the park.

Trees are coming back most dramatically in places where a browsing elk doesn't have a 360-degree view; these willows, for example, sit below a rise that blocks the animals' view. A look at the plants shows they have not been browsed at all in several years. Elk don't feel safe here, Ripple contends, because they can't see what is going on all around and are nervous about spending time in this vicinity. Just 50 meters away, however, where the terrain is level and wide open and the elk enjoy a panoramic view, the willows are less than a meter tall and have been browsed much more heavily

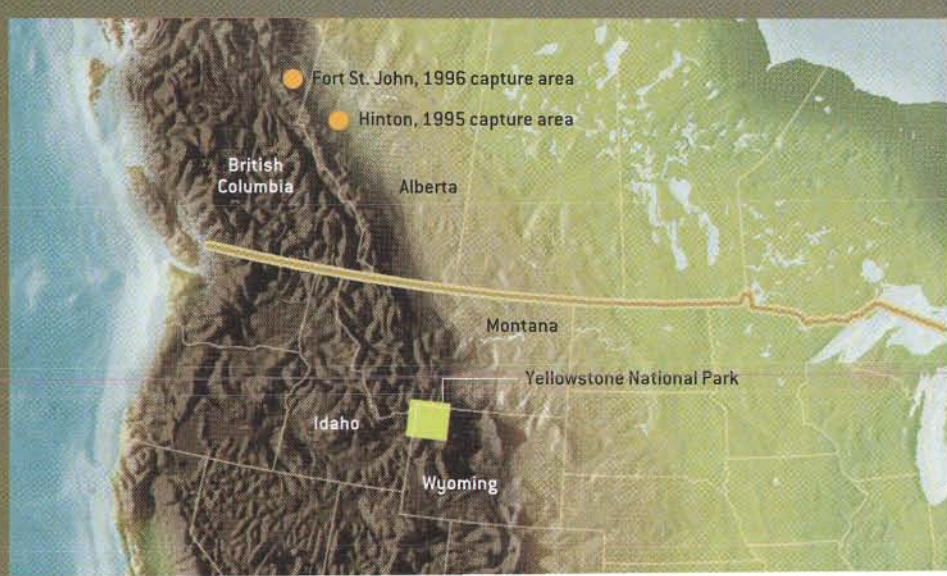
ONCE INSIDE YELLOWSTONE, sleighs transported Canadian wolves to isolated temporary holding pens.

IMPORTED WOLVES

To reintroduce the North American gray wolf into its former territory in Yellowstone National Park, wildlife biologists captured wolves from two areas in Canada (*map, below*) and transported them to the park. Why bring the animals across an international border when wolves in Montana are close at hand? Researchers had decided that the wolves most likely to succeed would be those that knew how to hunt Yellowstone animals. The Canadian wolves prey primarily on elk, which would be the major source of food in Yellowstone; the wolves from nearby states kill mostly deer.

The 31 wolves, brought in separate shipments in 1995 and 1996, spent the first two months in their new home in isolated acclimation pens roughly an acre in extent. Contact with humans was minimal to prevent the wolves from becoming habituated to people, even though wolves seldom develop such behavior (often seen in grizzlies). The goal was to release social units that could become breeding packs rather than individual wolves. At the same time, biologists wanted enough genetic diversity to avoid inbreeding problems, which is why they chose animals from several packs in two different Canadian provinces.

All the planning seems to have paid off as hoped. By the end of 2003 the newcomers had formed 16 packs, with a total population of about 170. Less than a decade after reintroduction, the government is moving to end federal protection for the wolf under the Endangered Species Act, a process known as delisting. Nearby ranchers, whose livestock make easy prey, hope to see the wolves delisted as soon as possible. Some advocates for the wolf, however, believe that protection is still necessary—the latest wrinkle in the old controversy between ranchers and supporters of wildlife.



NATIONAL PARK SERVICE (*photograph*); LUCY READING AND NINA FINKEL (*map*)

ELK COW WITH CALF is alert for wolves in the vicinity. Since wolves have been reintroduced into Yellowstone, many more calves are lost each spring to predation, and the overall elk population is roughly half what it was just before the wolves returned.

COYOTE AND MAGPIES feed on an elk calf killed by wolves. These animals, usually joined by ravens, often scavenge the remains of wolf kills, bringing to mind the classic progression on the African savanna of lion, hyena and vulture.

over the past three years. "It's the ecology of fear," Ripple says.

The Long Reach of the Wolf

OTHER CHANGES accompany the regrowth of vegetation taking place along the Lamar. Just upstream is a small beaver dam, one of three—the first dams documented on the river in 50 years. Slough Creek, a tributary of the Lamar, has six dams. Both Ripple and Smith believe that because of the regrowth, beavers have something to eat again. "Their food caches are full of willow," Smith says. And other changes are in the offing. As more woody vegetation grows along the Lamar, it will stabilize the banks and stop some erosion. More vegetation, Ripple predicts, will also shade and cool the stream. It means, too, more woody debris in the Lamar, which will slow the river, cause water to pool, and improve the trout habitat, leading to more and bigger fish.

Although the scientific focus so far has been on vegetation, the wolf seems to have an incredibly long reach into other parts of the Yellowstone food web as well. One of its most dramatic effects has been on coyotes. For three years before the reintroduction of wolves, Robert Crabtree, now chief scientist at the Yellowstone Ecological Research Center, a nonprofit organization based in Bozeman, Mont., and his wife, Jennifer Sheldon, who are both canid biologists, gathered baseline data on the park. Coyotes, they have found, have sacrificed a great deal to make room for the much larger wolves.

The number of coyotes in the park is down 50 percent and in core wolf areas has dropped 90 percent. Male coyotes are smaller than they were before the wolves arrived, perhaps, Crabtree says, because "the larger ones were more aggressive and challenged the wolves and lost." With fewer coyotes, their prey—voles, mice and other rodents—have exploded in number. That has benefited red fox and raptors. But red fox prey on songbirds as well, and more foxes could mean a greater toll on birds.

Wolves have also thrown the doors to the Yellowstone meat market wide open. Rarely do grizzly bears or cougars attack full-grown elk, although they eat calves or feed on the winter-killed carcasses. Wolves, on the other hand, pull down big ones all the time. After they eat their fill, they wander away, meat drunk, to sleep it off, or they get pushed off the kill by a grizzly. The presence of wolves has meant that much more meat is available on the ground. All manner of scavengers make a living on these carcasses, and an increase in numbers of everything from grizzly bears to magpies reflects these newfound riches. The largest number of ravens on a wolf kill ever recorded (135) was here. "We see bald eagles, golden eagles, coyotes, ravens and magpies on every kill that's made," Smith says. "I don't know what they did before wolves showed up."

But are wolves really the engine driving these changes? Most scientists think so. Smith says that "wolves are to Yellowstone what water is to the Everglades"—the primary force shaping the ecosystem. In Banff National Park in Canada, scientists have documented changes brought by wolves that returned on their own in the 1980s: willows reappeared, the diversity and abundance of songbirds doubled. Now researchers are coming to Yellowstone to tease out some of the first evidence of the impact that wolves are having on areas near the riverbanks; at least six projects are gathering data.

Some researchers, however, are agnostic about the effects of the wolf. Crabtree, for example, says that yes, willows are rebounding and imaging data show the regrowth dramatically. But a strong correlation between the return of wolves and the new growth is far from demonstrated. "Claiming wolves are responsible verges on bad science," he states. "The ecosystem in Yellowstone is a multicausal interactive system, and there's never a single cause. Even a predominant cause is rare. At the same time the wolf numbers were coming back, there was flooding along the river, and the climate is a lot warmer. Wolves probably have a role, but it is confounded by those factors. It will take 20 years or more before we know definitively."

Duncan Patten is a research ecologist who served on a National Academy of Sciences study of Yellowstone published in 2002. Yellowstone has not had a hard winter since wolves reached high levels, he observes, and elk may not have needed to resort to trees for food: "When win-

JESS R. LEE [*left*]; DONALD M. JONES [*right*]

VEGETATION in the park is rebounding because of decreasing numbers of elk. These mature cottonwood trees are now reinforced by seedlings and saplings that, without the overabundant elk, can grow to maturity.

BEAVERS have been lured back to the park by lusher vegetation, especially booth willows. The animals have built ponds that encourage still more vegetation to grow and have altered the course of some streams.

DIANE HARGREAVES (*left*); DONALD M. JONES (*right*)

ters are hard, elk take a lot of chances to put something in their belly. Give me two hard winters in a row, and I'll buy the argument."

The debate over the wolves' influence on the elk is fanning a long-standing argument over the proper way to manage Yellowstone's elk. At one time the park service also believed elk were too numerous and in the 1960s sent rangers to trap and shoot them by the thousands in a program called "direct reduction." By the end of the decade the total number of elk was down to an estimated 4,000. Public outcry ended the shooting, and in the 1970s the park service adopted a policy of natural regulation in wilderness parks such as Yellowstone, a management philosophy that would lift the heavy hand of humans and manage the parks as "vignettes of primitive America." Ever since, the elk numbers have climbed.

For decades now, critics, including the state of Montana, have denounced the National Park Service for allowing so many elk to crowd the vast stretch of native grasses. Letting nature take its course in what is a decidedly unnatural situation is folly, the critics argue. Few elk would spend the winter at such a high altitude, they add, if the animals could migrate onto the plains. Instead hunting pressure in the surrounding area compresses them into the park.

Some researchers assert that the return of vegetation along the riverbanks—brought on by a reduction in the number of elk—undermines the long-running contention of the park service that Yellowstone's elk population is within natural limits. But Smith defends the park's view and suggests that there are other ways to look at the situation. Elk numbers are going to fluctuate wildly over time, he says, and although numbers might have been, and still are, high, "they're within natural limits over the long term."

Countering this defense, Alston Chase, author of the 1986 book *Playing God in Yellowstone*, which was harshly critical of the policy of natural regulation, says for the park service to make such an argument is absurd. He found little evidence of large elk populations on the Yellowstone Plateau in the past. Between 1872 and 1920, he points out, the park was established, poaching was stamped out, the Native Americans were evicted, and the U.S. Biological Survey was killing wolves. That is when elk numbers started to soar—and it was a wholly unnatural irruption.

Unwitting Restoration Biologists

ALTHOUGH THE JURY is still deliberating the effects of wolves, early evidence strongly suggests that the canids are unwitting restoration biologists. By simply doing what they do—mainly preying on elk—they are visiting great changes on the Yellowstone ecosystem. Many of the changes are positive for those things humans value, and for experts to accomplish some of these same goals would be hugely expensive.

Wolves have brought other lessons with them. They dramatically illustrate the balance that top-of-the-food-chain predators maintain, underscoring what is missing in much of the country where predators have been eliminated. They are a parable for the unintended and unknown effects of how one action surges through an ecosystem. More important, the Yellowstone wolves are bringing into focus hazy ideas of how ecosystems work in a way that has never been so meticulously documented. Just as the actions of the wolf echo through Yellowstone, they will reverberate into the future as they help to increase the understanding of natural systems. SA

Jim Robbins is a freelance journalist based in Helena, Mont., who writes about the changing American West for the New York Times *and other publications.*

MORE TO EXPLORE

Yellowstone after Wolves. Douglas W. Smith, Rolf O. Peterson and Douglas B. Houston in *BioScience*, Vol. 54, No. 4, pages 330–340; April 2003. Available at **konstanza.ingentaselect.com/vl=4060996/cl=73/nw=1/rpsv/cw/aibs/00063568/v53n4/s8/p330**

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Yellowstone National Park Wolf Information is at **www.nps.gov/yell/nature/animals/wolf/wolfup.html** and **www.ypf.org**

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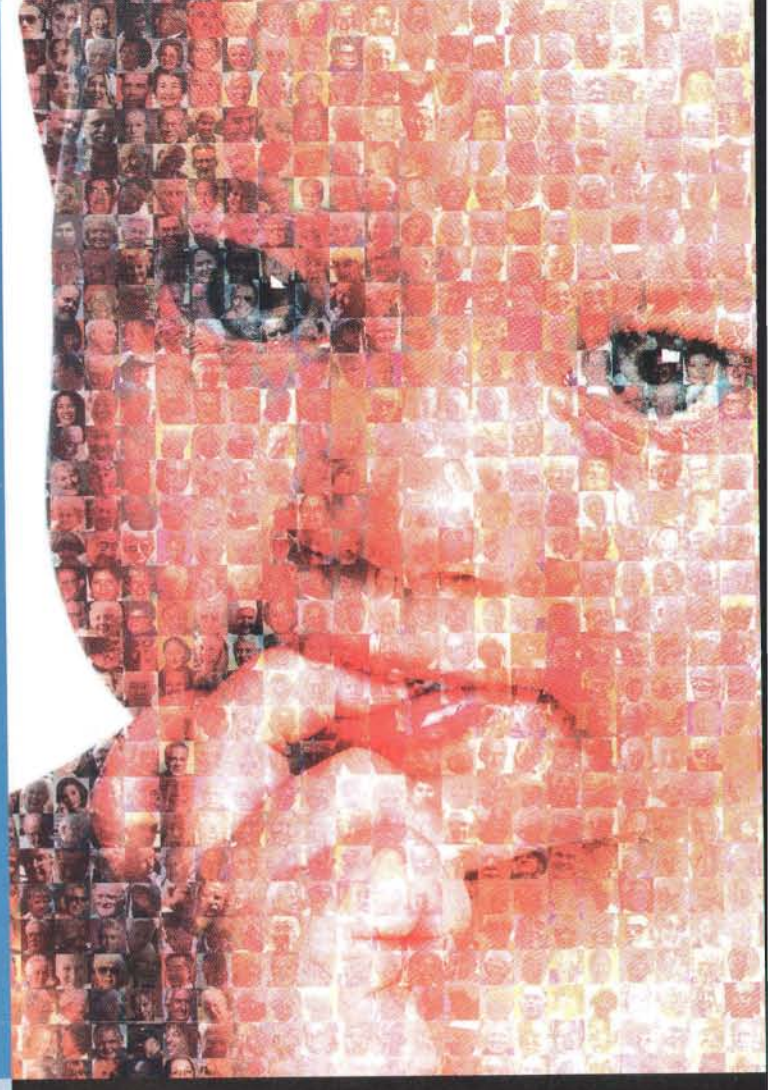

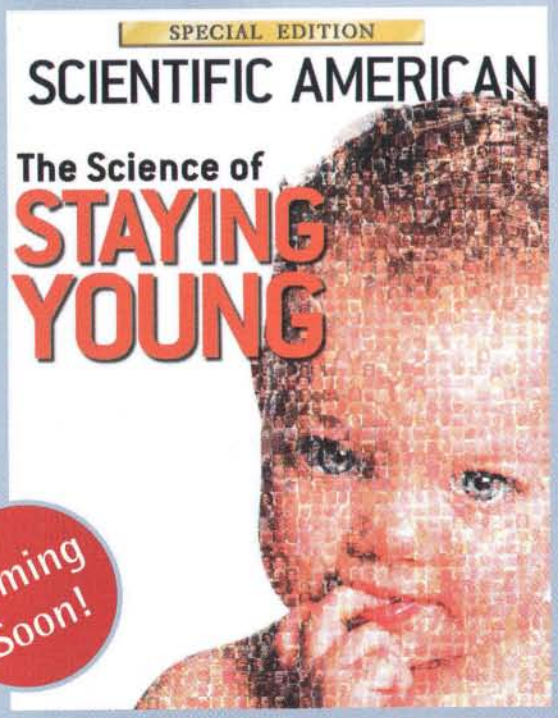

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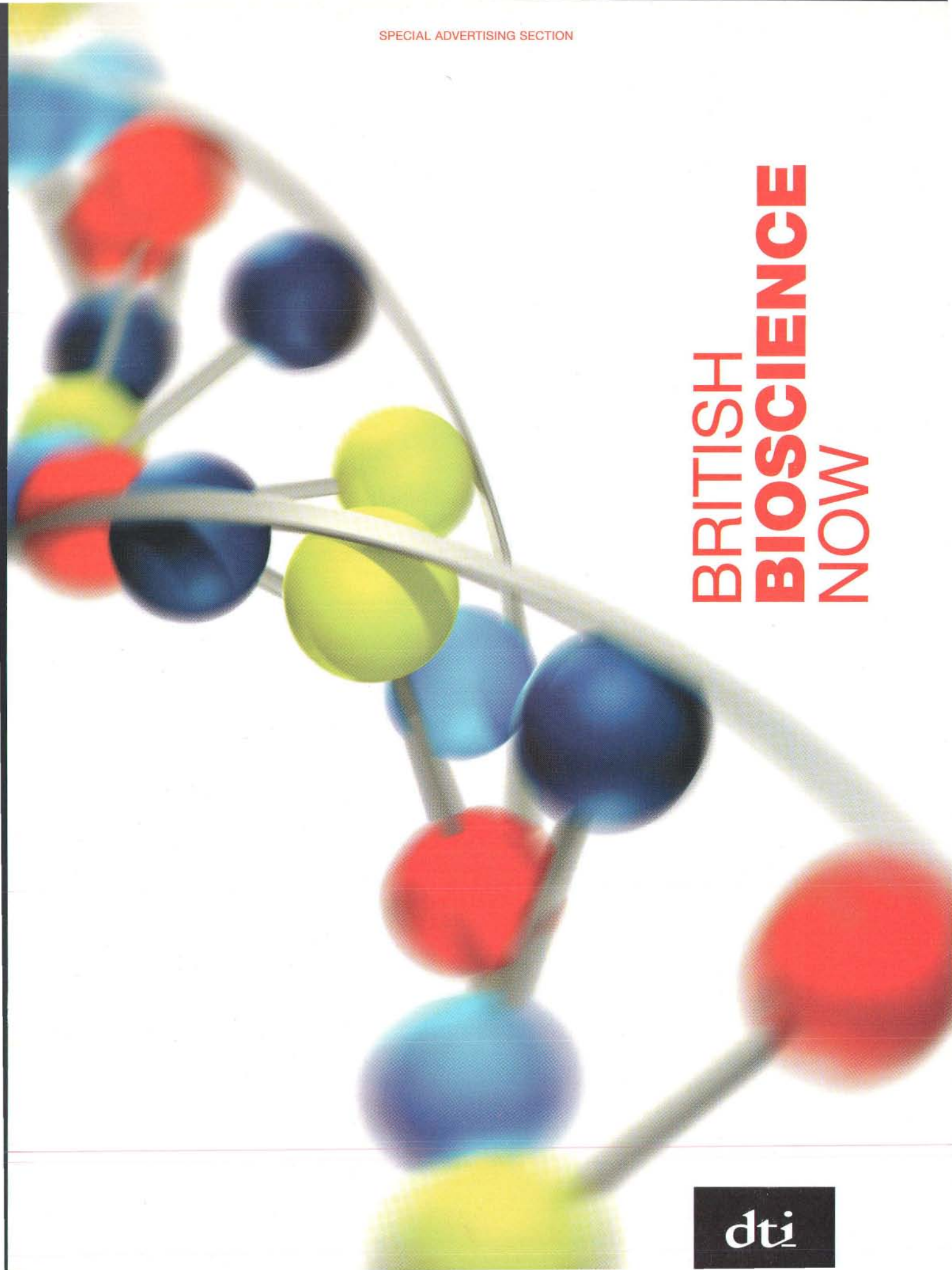

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"We need a modern industrial base, doubling investment in science, leading Europe in the biosciences and technology, more high-tech spin-offs from universities than ever before – not just world beating British ideas but world beating products, British profits, British jobs." Tony Blair, Prime Minister (Labour Party Conference speech, 2003)

Bioscience in the UK

2003 was a memorable year for UK bioscience. From the discovery of the double helix structure of DNA in 1953 in Cambridge, to our contribution to the international human genome sequencing project, completed in 2003, the UK has been a leader in bioscience.

The celebrations in the UK of the 50th anniversary of the DNA structure discovery provided a reminder of the significant contribution this technology and this country have made and are making to society. It also proved a positive year for industry, with encouraging signs that investors are becoming more willing to back high-quality bioscience companies.

In March 2004, Government outlined its commitment to make the UK one of the most competitive locations in the world for science, research & development and innovation. A ten-year investment plan, to be announced as a central priority for this summer's *Spending Review*, will be backed up with plans for a fundamental review of funding needs and policy priorities for science, engineering and innovation.

The UK bioscience sector is already well placed to benefit. We are at the forefront of innovation, and our pharmaceutical and biotechnology industries are major global players. The UK offers world-class R&D and an abundance of skilled staff, combined with a sound approach to regulation and strong Government support.

The UK – Europe's leader in bioscience

The UK is one of the best places in the world for bioscience business and enjoys significant strengths supporting innovation in healthcare, agriculture, industry and the environment.

Aided by an environment with a high degree of commercial flexibility, the UK is home to dynamic, research-based pharmaceutical and biotechnology industries that are the most productive in Europe.

Accounting for just under half of all European biotechnology companies, the UK's sector is the largest in Europe and second globally only to the USA. The UK has 480 specialist bioscience companies, employing around 26,000 people with revenues of over €6.4 billion in 2002. Our biotechnology industry, because of its maturity, has come through the recent tough times probably better than anywhere else. In 2002, UK companies secured about 41% of the European venture capital for biotech.

The UK is also the sixth-largest pharmaceutical market in the world and the world's largest exporter of pharmaceuticals in 2002. In 2001, R&D spending accounted for 27% of the European total, well ahead of its competitors. The UK is second only to the USA in the number of new drugs that have been discovered and developed in its laboratories. The productivity of drug discovery, by patents filed per dollar invested, is higher than any other G7 economy.

The long-term presence of some of the world's leading pharmaceutical and biotechnology players within the UK has encouraged the growth of an exceptionally broad and experienced support services sector, including R&D, manufacturing, logistics and sales and marketing. These factors combine to make the UK an exceptionally promising marketplace – either for dedicated biotechnology or multinational pharmaceutical companies looking to gain competitive advantage through investing in a growing sector.

UK biotechnology products at all phases of clinical trials account for 43% of biotechnology drug candidates from all European public companies. More than 194 biotechnology-based drug candidates are in development, with 23 of these now at Phase III clinical trials, accounting for 43% of those from European biotechnology companies at this stage. There are 42 products marketed by UK bioscience companies that were developed and/or invented in the UK.

The ongoing revolution in medical bioscience is enabling diagnostics to come of age, creating exciting opportunities in disease treatment and prevention. The UK medical devices industry is highly innovative, with hundreds of start-up companies and strong links with an exceptional engineering and science base. UK researchers are playing a key role in technological advancement in biomarkers and DNA probes

Biobank website: **www.ukbiobank.ac.uk**
Sanger Institute website: **www.sanger.ac.uk**
European Bioinformatics Institute website: **www.ebi.ac.uk**
Office of Science & Technology website: **www.ost.gov.uk**

Above: **In 2003, *'Bioscience 2015: Improving National Health, Increasing National Wealth'*, was published by the Bioscience Innovation & Growth Team (BIGT).**

for vascular disease, cancer and infectious diseases, genetic testing and pharmacogenetic screening.

The UK also possesses a well-developed and growing industrial biotechnology sector. These companies draw customers from various industry sectors and overseas sales account for at least 20% of the overall turnover.

A growing demand and market expansion – notably surface preparation, bio-cleaning and biosensors – has enabled the number of UK companies actively involved in industrial and environmental biotechnology to grow to an estimated 280 over the last 3 – 4 years.

Strong science

The root of the UK's continued success in the biosciences is the excellence of our science base. The UK is home to world-renowned research institutions, such as the *Sanger Institute* (a leading player in mapping the human genome), and the *European Bioinformatics Institute*.

The UK has received 47 Nobel Prizes in the last 50 years and continues to rank second in the world with 11% of global citations. UK universities are noted for high-quality teaching and research in chemical, biological and molecular science and technology. Over 20% of all university graduates gain degrees in medical or natural sciences, enabling pharmaceutical and biotechnology companies to access a wealth of world-class talent. And this world-class science and expertise is being translated into innovation, jobs and prosperity for the UK.

Strong links between university research departments and industry, encouraged by successful Government initiatives, help companies to access and exploit leading-edge research. New start-up ventures have been strategically placed in clusters around some of the UK's leading universities with the help of Regional Development Agencies (RDAs).

213 spin-outs were established in 2001/2 and income from licensing of IP increased by 83% to £33 million. HEIs also filed 967 patents in 2001/2, an increase of 8%. Many of the Government's initiatives bring together public and private sector funding. This collaborative support ensures that the UK is able to create one of the best possible research infrastructures for the biosciences. One such project is the *UK Biobank. The Medical Research Council, Department of Health* and *The Wellcome Trust* are together providing an initial £45 million for the world's largest resource for the study of the causes and factors influencing health and disease.

Government support

The UK's outstanding science base is supported by Government's long-term commitment to bioscience. Recognising bioscience as a key industry for the future, the Government is committed to creating conditions conducive to the sector's growth and success, both in terms of research infrastructure and regulatory framework.

Government continues to increase research funding through the *Science Budget*. Following the 2002 *'Comprehensive Spending Review,'* this is set to grow an average of 10% a year in real terms and will reach £2.9 billion by 2006. As part of the *Science Budget*, over the next two years the Government is putting £1 billion into science infrastructure.

New ideas from the science base are only part of the wider process of innovation that is essential to wealth creation and quality of life. Following a review of innovation policy in 2003, the Government published its *Innovation Report 'Competing in the Global Economy: the Innovation Challenge'*.

The report outlines actions to do more to exploit the UK's excellent science base and track record in invention for commercial benefit. An R&D tax credit scheme has already been introduced, allowing companies to claim enhanced tax relief for their qualifying R&D spending.

A Government-led web portal, *i-bio*, also provides a single online resource for companies to navigate all aspects of the UK biotechnology regulatory process.

Vision for the future

The future of many areas of UK bioscience has been the subject of public-private strategic studies.

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i-bio website: **www.i-bio.gov.uk**
BIGT report weblink: **www.dti.gov.uk/bio-igt/bio-igt-index.html**
PICTF weblink: **www.advisorybodies.doh.gov.uk/pictf**
HITF weblink: **www.advisorybodies.doh.gov.uk/hitf**

The first of these, the *Pharmaceutical Industry Competitiveness Task Force (PICTF)*, brought together the expertise of UK pharmaceutical industry leaders with Government Ministers to ensure that the industry remains competitive within the global market. It focused on ensuring that the right strategies are in place to allow it to contribute fully to the economy and bring safe, effective medicines to the UK market.

In 2003, *'Bioscience 2015: Improving National Health, Increasing National Wealth'*, was published by the *Bioscience Innovation & Growth Team (BIGT)*. A collaboration with the UK's biotechnology sector trade association, supported by Government, it identified barriers to the growth of the bioscience sector in the UK. The report makes recommendations for action by both Government and industry so that by 2015 the UK will have secured its position as a global leader in bioscience.

Government has already set up initiatives to further investigate or implement many of these recommendations. Government has already announced plans to support a new *National Clinical Research Network* that brings private and public sectors and medical charities together, and confirmed that the combined budget for medical research and research and development within the NHS will rise, and by 2008, will approach £1.2 billion a year.

Addressing another significant healthcare area, the *Healthcare Industries Task Force (HITF)*, launched in November 2003, marks the beginning of a new strategic relationship between medical devices industry leaders in the UK, key Government Ministers and policy-makers.

The first collaboration of its kind between public sector and healthcare industry stakeholders, one of its goals is to foster and facilitate an improved environment for product research, development, clinical evaluation and related manufacturing for investment.

In June 2003, the *Department of Health* also published its £50 million genetics strategy for the *NHS*. The *Genetics White Paper, 'Our Inheritance, Our Future – Realising the Potential of Genetics in the NHS'* sets out the Government's commitment to developing genetics knowledge, skills and provision within the NHS to take maximum advantage of the safe, effective and ethical application of new genetic knowledge and technologies for all patients.

Outside the healthcare sector, an *Industrial Biotechnology Task Force (IBTF)* was established in December 2003, to help guide strategic investment in emerging technologies within industrial production. IBTF will scope the opportunities, identify barriers to commercial success and advise on measures to promote greater collaboration and growth.

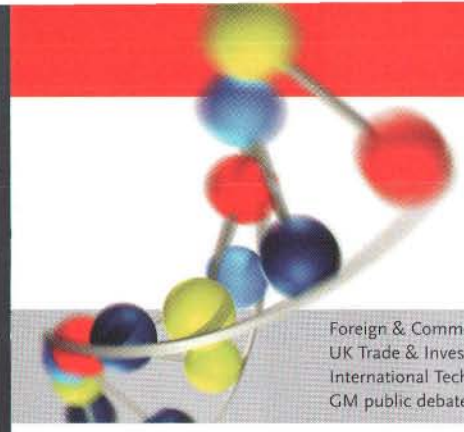
In March 2001, the *Government Industry Forum on Non-Food Uses of Crops* was set up to provide strategic advice to government and industry on the development of non-food uses of crops in the UK. A report in March 2004, *'Prospecting Bioscience for the Future of Non-Food Uses of Crops'*, identified opportunities for the UK to contribute to the global challenge of creating bio-refining technology platforms, including cultivation of high-value, low-volume crops for pharmaceuticals and novel specialist materials.

The right environment is vital

Creating the right regulatory environment is a key driver for creating a successful UK bioscience sector. Government works to ensure national and international regulations are proportionate, practical, enforceable and based on sound science, thereby avoiding bureaucracy that stifles business formation and growth.

An area where the UK has been successful in adapting legislation and regulations to changing circumstances is in the use of stem cells.

There has been an open, well-informed debate in the UK, involving public opinion formers and Parliament. This has resulted in the extension of the *Human Fertilisation and Embryology Act* to allow carefully regulated use of embryonic stem cells in research on understanding serious disease and development of treatments. The approval of these regulations has put the UK in a leading position internationally and has been instrumental in attracting top scientists to the UK.



Foreign & Commonwealth Office website: **www.fco.gov.uk**
UK Trade & Investment BioPartner weblink: **www.globalwatchonline.com/biopartner**
International Technology Promoters weblink: **www.globalwatchonline.com/itp**
GM public debate website: **www.gmpublicdebate.org**

GOVERNMENT MINISTERS ARE ADVISED BY STRATEGIC ADVISORY BODIES	ADVISORY BODIES WORK ALONGSIDE REGULATORY AND TECHNICAL BODIES
Human Genetics Commission (HGC)	Gene Therapy Advisory Committee (GTAC)
Human Fertilisation and Embryology Commission (HFEA)	Genetics And Insurance Committee (GAIC)
Agriculture and Environmental Biotechnology Commission (AEBC)	Advisory Committee on Releases to the Environment (ACRE)
Food Standards Agency (FSA)	Advisory Committee on Novel Food and Processes (ACNFP)

In March 2004, the Government set out its overall policy on genetically modified crops. GM crops will be assessed on a case-by-case basis, taking a precautionary and evidence-based approach, making the protection of human health and the environment the top priority. This approach was agreed following a rigorous and comprehensive assessment of the case for and against GM crops, including the results of a national *public debate*.

Together and separately, strategic advisory and regulatory and technical bodies (*see chart above*) have a policy of openness that permits free public access to the facts that inform regulatory decisions. This robust framework, combined with strong private and public funding, creates the supportive environment that enables talented UK scientists to remain at the cutting edge of innovation, and biotechnology to flourish.

International collaboration

The UK bioscience sector competes in a global market and international collaboration is increasingly important. *The Foreign & Commonwealth Office (FCO)* has established a new network of *Science & Technology* attachés to help capitalise on and enhance the UK science base, to help companies access overseas innovation and technology, to facilitate high-tech trade and attract foreign investment.

In 2003, the FCO, with the *British Council*, published '*DNA and After*' which tells the story of how the structure of DNA was unravelled, shows the enormous potential for biotechnology in the future and gives an overview of the work already underway in the UK.

UK Trade & Investment is the lead Government organisation supporting companies in the UK trading internationally, and overseas businesses seeking to set up or expand in the UK.

In 2003, UKTI set up a new *Biotechnology and Pharmaceuticals* team in Cambridge. UKTI's *BioPartner* website holds searchable information about UK companies and research organisations interested in collaborating with overseas partners.

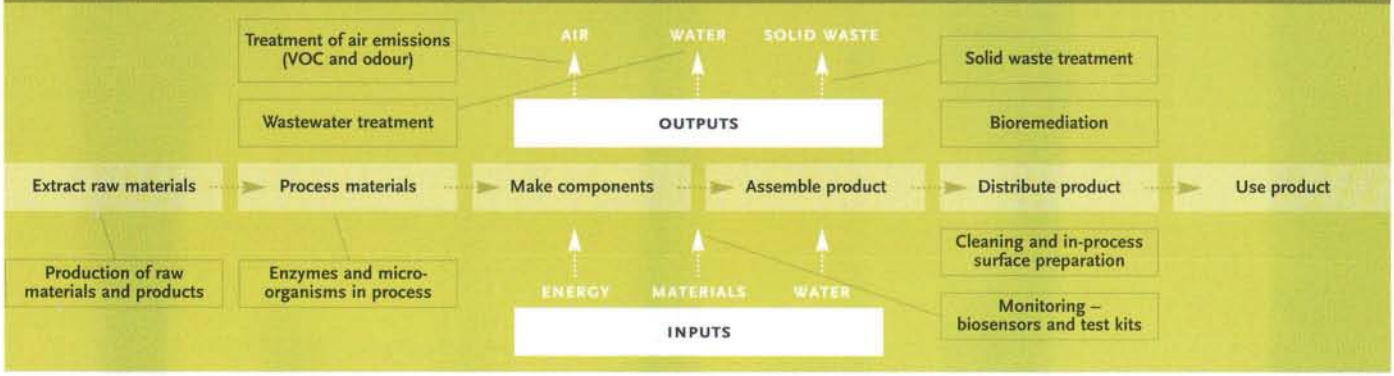
The Government is keen to encourage international collaboration of UK scientists and UK high-tech companies. We have a strong network of *International Technology Promoters* who have the task of helping UK biotechnology companies access overseas technology and form partnerships with overseas companies, and we see biopartnering as a major element of the future success of the sector.

This *Scientific American* special advertising section gives just a snapshot of the work that is going on in bioscience in the UK today.

dti Improving industrial competitiveness through biotechnology

BIO-WISE website: **www.dti.gov.uk/biowise**
EuropaBio website: **www.europabio.org**

APPLICATIONS OF BIOTECHNOLOGY DURING THE MANUFACTURING PROCESS



Some of the UK's, and the world's, most successful, vigorous and innovative industries – pharmaceuticals, healthcare and food and drink, for instance – already rely on biotechnology. Now, other key sectors such as chemicals, engineering, agriculture and environmental technology are joining in the move toward a bio-based economy.

Cleaner, smarter manufacturing

Biotechnology can deliver solutions to the twin challenges of competitiveness and sustainability at every stage of the manufacturing process, from raw materials through to end-of-pipe and clean-up (*see diagram*).

Real benefits for all

Worldwide, *OECD* estimates current business benefits from biotechnology amount to €100 billion. But the advantages are more than just economic. Workers, communities and the environment benefit from less polluting, less hazardous, less energy-intensive industrial production. For example, degreasing metal components with enzymes instead of organic solvents reduces costs, energy demand, workplace hazards and waste.

Excellent science, successful suppliers, growing markets

The UK's supportive economic and political conditions provide an enviable platform for research, development and commercialization of industrial biotechnology.

The UK's talented research community has internationally-recognised centres of expertise and established technology transfer mechanisms, with strong links to the supplier base of over 100 companies and networks of experienced investors, enabling efficient innovation and growth.

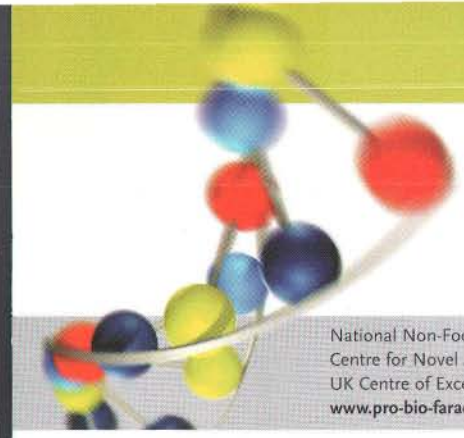
Successful commercial specialisations include: renewable feedstocks, biomaterials, enzyme production, biosensors, biocleaning, surface coating, product authentication, waste treatment and remediation technologies. The UK is also home to some of the world's largest, most forward-thinking industry customers and is one of the world's most open markets, investing in almost every country in the world: over 70% of UK suppliers already export goods and services to Europe, Asia and the Americas.

Driving the European agenda

International co-operation plays an important part in successful innovation and technology transfer. The UK plays an active role in international collaborations to advance industrial biotechnology, such as *EuropaBio's 'White'* biotechnology initiative (**www.europabio.org**).

Future developments

Looking to the future, an *Industrial Biotechnology Task Force* has recently been established to guide UK investment in the area until 2015 – a reflection of the UK's commitment to competitive sustainable development.



Biotechnology has become an engine of the global economy

National Non-Food Crop Centre website: **www.nnfcc.co.uk**
Centre for Novel Agricultural Products website: **www.cnap.org.uk**
UK Centre of Excellence for Biocatalysis website: **www.pro-bio-faraday.com**
UK Centre of Excellence for Remediation of the Polluted Environment website: **www.firstfaraday.com**
Genesis website: **www.genesis-faraday.org**

BIO-WISE is the Department of Trade and Industry's programme to stimulate adoption of industrial biotechnology.

CASE STUDIES

UK case studies reflecting the capability and success of industrial biotechnology can be found at the BIO-WISE website (www.dti.gov.uk/biowise) together with a supplier database. Two brief examples are:

BIOTECHNOLOGY IMPROVES PRODUCT QUALITY

WJ & W Lang Ltd **invested an enzyme-based process for de-hairing leather hides, enabling them to produce larger, flatter and more uniform hides. The higher quality product also helped their customers obtain an even finish when the leather was dyed. Annual cost savings in materials and waste disposal were over €500,000.**

ENZYME CLEANERS HELP SOLVENT COST EVAPORATE

Enzyme-based biocleaners have successfully replaced hot caustic solutions and vapour degreasing techniques for surface cleaning of metal components. For example, ***Expert Heat Treatments*****, found that using an enzyme cleaner instead of vapour degreasing preserved product quality while reducing unit cleaning costs by 60% and annual running costs by 74%, equivalent to over €22,000 pa. Further, the capital investment needed for an additional cleaning line to enable the firm to expand was more than halved, giving a payback time of less than four months.**

The DTI's BIO-WISE programme has supported 21 demonstrator projects showing the benefits of innovative biotechnology solutions in real industrial situations. Details can be found at the BIO-WISE website (**www.dti.gov.uk/biowise**).

Investment in the area includes national institutes such as the National Non-Food Crop Centre as well as public/private partnerships and development networks.

THE UK: A LEADING CENTRE OF INDUSTRIAL BIOTECHNOLOGY

The UK science base encompasses all principal areas of industrial biotechnology: biomaterials, bioprocessing, bioinformatics, genomics, high-throughput technologies, animal health, agriculture, biopesticides, food technology, marine biotechnology, biodiagnostics for monitoring and control and bioremediation.

PUBLIC/PRIVATE PARTNERSHIPS

Centre for Novel Agricultural Products: **exploring the potential of industrial products from plants.**

UK Centre of Excellence for Biocatalysis**: bringing together 48 companies, 35 universities and research institutes and six intermediaries to focus on advanced biotechnology for the chemical and pharmaceutical industries.**

UK Centre of Excellence for Remediation of the Polluted Environment **at Oxford: focusing on innovative assessment, remediation and management technologies.**

NETWORKS AND PARTNERSHIPS

A ***National Biomanufacturing Centre*** **is under development.**

Genesis: **genetics and genomics research for the UK's animal breeding and animal health industries.**

Beacon Bio: **creating exploitation platforms for a range of industrial and environmental biotechnologies (eg. biosensors, bioremediation).**

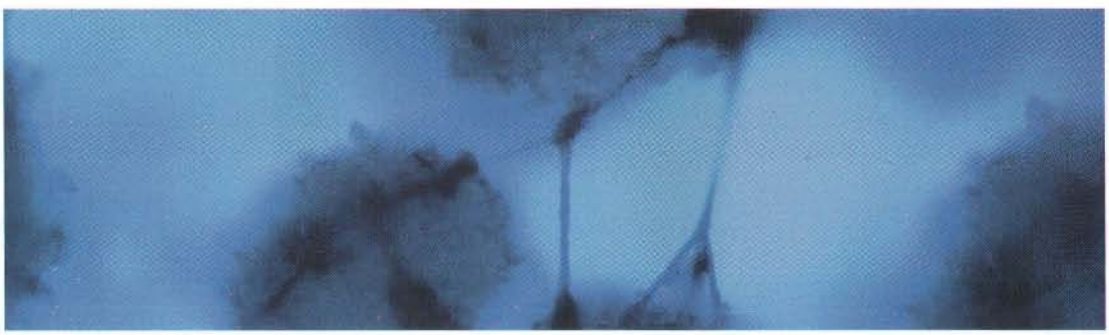
Industrial biotechnology also has a place in the UK nanotechnology programme.

bbsrc
biotechnology and biological sciences research council

MRC Medical Research Council

British biotech: Building on a great tradition

BBSRC website: **www.bbsrc.ac.uk**
MRC website: **www.mrc.ac.uk**



Human bone-forming cells growing on granules of calcium phosphate.
© JA Hunt and J Gallagher, *UK Centre for Tissue Engineering, University of Liverpool*

Bioscience research in Britain has a strong tradition, but an even brighter future. Scientists working in its excellent universities and research institutes have been at the vanguard of scientific discovery for generations. Today, the strength of Britain's research community in key emerging areas, such as post-genomics, stem cells and bionanotechnology, places British bioscience in an extremely strong position to build upon its reputation for excellence in research, discovery and innovation.

Working together

Public sector funding of research in Britain has done much to create this advantageous position. Working together, the *Biotechnology and Biological Sciences Research Council (BBSRC)* and the *Medical Research Council (MRC)* have helped build strong communities of researchers, through support for research and innovation in universities and research institutes, and the training of high-quality bioscientists.

Notable BBSRC advances include the work that led to the cloning of Dolly the sheep; insights into the biology of stem cells; contributions to the world's first genome sequence of a plant – *Arabidopsis*; the sequencing of nature's antibiotic factory *Streptomyces coelicolor*; and the development of the world's first robot scientist capable of generating hypotheses and conducting experiments.

The MRC has been responsible for many revolutionary breakthroughs in biomedical science. These include characterising the three-dimensional structure of protein and DNA, and the development of protein and DNA sequencing, monoclonal antibodies, magnetic resonance scanning and confocal microscopy.

Leading Europe in biotech

Against this background, the UK has developed the strongest biotechnology industrial sector in Europe. Support from the Research Councils has been crucial to developing the skills and facilities that British researchers need to turn scientific discoveries into commercial opportunities.

Ten of the spin-off companies formed through the BBSRC/MRC *Bioscience Business Plan Competition* have now raised £2.3 million investment and 14 companies have received research contracts totalling £2.8 million through the BBSRC's *Small Business Research Initiative*.

Over the last four years, the MRC's technology transfer company, *MRC Technology*, has earned over £60 million in licensing income and entered into 150 licensing agreements with industry.

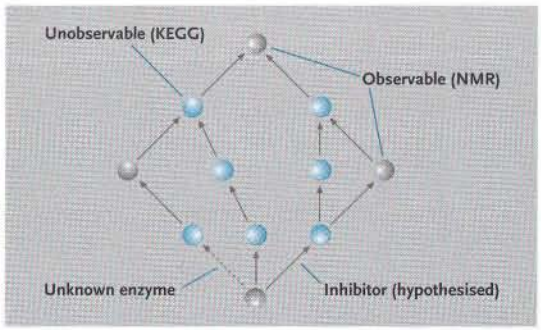
Two of the largest UK biotech companies, *Celltech* and *Cambridge Antibody Technology*, originated as start-ups based on MRC technology.

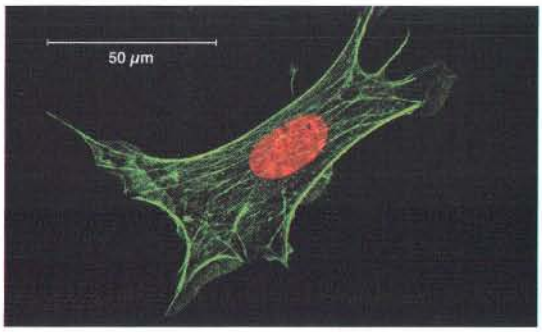
Add world-class facilities such as the *Babraham Bioscience Incubator*, and the knowledge transfer expertise available through MRC Technology and *Plant Bioscience Ltd*, and it is clear that the UK is as excellent a choice for biotechnology as it is for bioscience research.

dti Beacons

The DTI Beacon Projects: An innovative approach to delivering exciting, industry-targeted science and technology

The Beacon Projects website: **www.beaconprojects.org.uk**





Right: **The Metalog project (Imperial College London) is using Inductive Logic Programming (ILP) to fill 'gaps' in biochemical network descriptions.**

Far right: **Mouse 3T3 cell, grown in tissue culture and stained for DNA (in red) and for the cytoskeletal protein actin (in green).** Courtesy of Dr DG Spiller, *University of Liverpool*

The Beacon Projects are a UK-wide group of interdisciplinary, high-risk projects with a strong industrial thrust, funded by the *DTI*. They cover a diverse mix of exciting, world-class research areas which combine cutting-edge science with great potential to deliver wide-ranging benefits to industry.

Functional bio-imaging using fluorescence lifetime imaging

Physicists, medical researchers and other researchers are working to deliver a functional imaging technology platform for use across a wide range of biomedical, pharmaceutical and clinical problems, including *real-time diagnosis and monitoring of diseases.*

Vertical integration across biological scales – towards in silico organs for computational physiology

Biologists, engineers, mathematicians and computer scientists are integrating models at different levels of biological organisation with the long-term objective of building an in-silico model of the liver, paving the way for *novel approaches to understanding how diseases develop and for finding new drugs.*

Genomic nanoprocessors – creating a platform technology for bio-intelligent medication

Developing DNA devices that respond to electronic and biochemical signals and which can be integrated onto a silicon chip, leading to development of *devices that can detect disease in vivo.*

Metalog – integrated machine learning of metabolic networks applied to predictive toxicology

Expertise in computational and structural bioinformatics and metabolic research is being applied to developing a machine learning-based computing tool – 'Metalog' – to predict toxicity. *Application in the pharmaceutical industry for screening of toxic compounds could transform the drug development process.*

Software tools for the simulation and analysis of biochemical networks

A computer modelling-based approach to understanding biochemical networks, the focus of many drug discovery efforts, is being taken with the aim of developing *a user-friendly computing tool for the simulation and analysis of a diverse range of biochemical networks.*

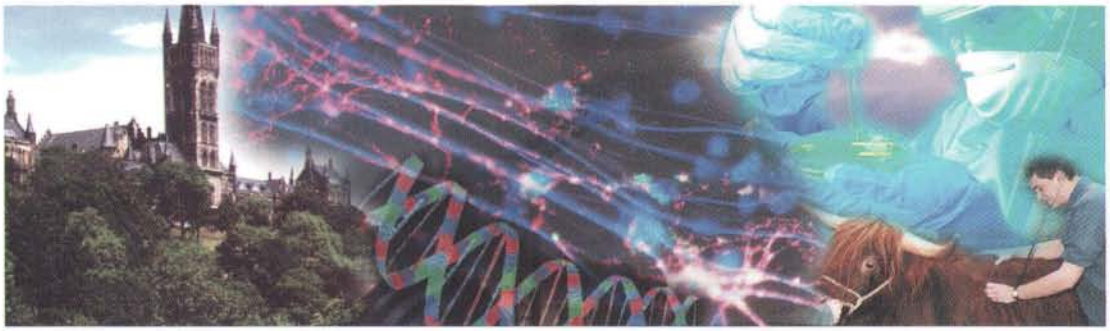
High throughput analysis of gene function in mammalian cells

This project aims to develop a high-throughput platform for functional gene analysis using an innovative approach based on live cell imaging. Such an attractive and timely tool for basic and applied biomedical scientists *will lead to a faster drug development process.*

Although primarily aimed at the pharmaceutical and biotechnology industries, there will be benefits to other industrial sectors from the advances gained by these projects. Companies and industrial scientists are encouraged to visit **www.beaconprojects.org.uk**

Bioscience at the University of Glasgow: From bench to bedside

University of Glasgow website: **www.gla.ac.uk**
University of Glasgow bioscience weblink: **www.gla.ac.uk/bioscience**



Glasgow's bioscience: a proud past, and strong investment in creating an exciting future. Scotland's University of Glasgow was founded in 1451 and has been delivering research excellence for 553 years.

Delivering significant, measurable improvement in health and quality of life is the fundamental objective of the *University of Glasgow's* rich resource of biomedical scientists. Biomedical science in the post-genomic era presents new, far-reaching opportunities to harness and translate knowledge for the benefit of society. In pursuing this agenda, our scientists are tackling two key challenges: the novel use of sophisticated molecular and structural techniques to address whole organism biology and the application of such techniques to deliver benefits to humans and animals. These challenges require multidisciplinary approaches so the *Faculties of Biomedical & Life Sciences, Medicine* and *Veterinary Medicine* are working closely together to tackle them in a focused plan of development.

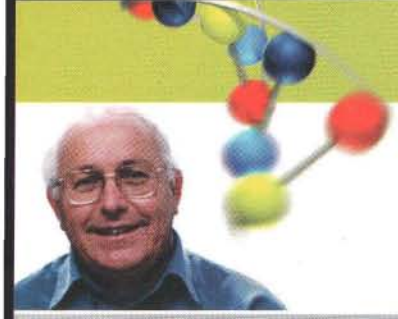
Our new *Biomedical Research Centre* will bring together 20 leading biomedical research groups in three cognate areas – *Structural Biology, Molecular Parasitology* and *Immunobiology* – and link them to clinical researchers. The aim is to create and increase extensive multidisciplinary research, seeking solutions to problems of diseases of major morbidity and mortality and applying this knowledge rapidly in the clinic. The adjacent *BHF Cardiovascular Research Centre* will focus our research in cardiovascular functional genomics, contributing to the development of new methods of detection and prevention of diseases of the heart and blood vessels. The scientists in these new buildings will be supported by our new joint *Functional Genomics Research Facility* and our new *Bioinformatics Research Centre*. Formal links with hospitals facilitate streamlined clinical trials, ensuring delivery from bench to bedside.

Another new state-of-the-art development at the *Cancer Research UK Beatson Institute* will transform Scotland's cancer research environment. The institute will provide world-class facilities for 400 researchers tackling cancer from research into the fundamental biology of cancer cells to the development of new targeted treatments.

Researchers at the *AVMA*-accredited *Veterinary School*, housed in the *Institute of Comparative Medicine*, have linked with engineers and computing scientists to break the boundaries of translational research with applications for improved animal and human disease diagnosis and prevention. Internationally-acclaimed work on FIV, a strong example of our excellence in virology and oncology, has established links between viruses and tumours, resulting both in the development of life-saving vaccines for animals and humans and new diagnostics. Developments across our themes of excellence are nurtured, and the institute now houses rapidly expanding groups on infectious diseases epidemiology committed to improving animal and public health and reproductive biology.

These initiatives, and parallel developments in plant science and ecology including the modernisation of the *University Field Station* at Loch Lomond, are all contributing to our agenda for delivering a healthy and sustainable future.

Contact us at **www.gla.ac.uk/bioscience**



Dundee: The hub of biosciences and biotech in Scotland

Sir Philip Cohen
ROYAL SOCIETY RESEARCH PROFESSOR AND DIRECTOR OF RESEARCH *School of Life Sciences* AND MRC PROTEIN PHOSPHORYLATION UNIT *University of Dundee*

University of Dundee website: **www.dundee.ac.uk**
School of Life Sciences weblink: **www.dundee.ac.uk/lifesciences/**
Research and Innovation Services weblink: **www.dundee.ac.uk/research/welcome.htm**
School of Medicine weblink: **www.dundee.ac.uk/medicalschool/**

Right: **The Wellcome Trust Biocentre at the School of Life Sciences, University of Dundee.**

Far right: **Upstate, Dundee. The current building is on the left and the second building, under construction, is on the right.**

Bioscience at Dundee

Dundee is at the centre of a growing biotechnology hotspot, fuelled by the world-class research at the *University of Dundee* and accelerated through innovative links with industry and, crucially, the backing of the economic development agency, *Scottish Enterprise*. The sector has now gained momentum and a cluster of specialist supply and service companies have been spawned or relocated to Dundee. These include spin-off companies, clinical trials and diagnostics companies. Over 2,500 people are employed directly in the biosciences and biotechnology, making Dundee the third largest biotech cluster in Britain, after Cambridge and the Thames Valley region. This sector accounts for 14% of the local economy.

Bioscience at the University of Dundee

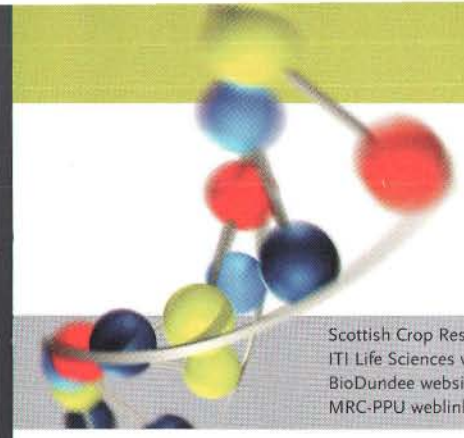
Papers published by University of Dundee scientists in biology and biochemistry were quoted more frequently over the past ten years than those from any other European university *(ISI Essential Science Indicators, Philadelphia)*. The university was also voted the third-best scientific institution to work in outside the USA (*The Scientist*, October 2003).

University Vice Chancellor Sir Alan Langlands was previously chief executive of the English *National Health Service*, while Chancellor Sir James Black, the 1988 Nobel Laureate for Medicine, started his career as a Dundee Faculty member in 1946. Protection and marketing of the university's intellectual property is carried out by its technology transfer section (*Research and Innovation Services*).

The *School of Life Sciences* is the hub of the biosciences, with major strengths in cell signalling, developmental and environmental biology, gene regulation, immunology and molecular parasitology. Comprising seven research divisions, its 600 scientists and support staff from 54 countries include two of Britain's 18 *Royal Society* Research Professors. It is also home to the *Division of Signal Transduction Therapy*, a unique collaboration with six of the world's largest pharmaceutical companies, and one of the largest-ever research collaborations between pharma and a British university.

Cancer research is a great strength of the *Schools of Medicine and Life Sciences*. Substantial support from *Cancer Research UK*, other cancer charities and the *Medical Research Council* is combined with impressive local fundraising efforts, by the *Ninewells Cancer Campaign* and *Tenovus Tayside*, to drive this forward.

Dundee is a global player in diabetes research. Scientists in the School of Life Sciences worked out how insulin stimulates the conversion of blood glucose to its tissue storage form (glycogen) and identified the enzyme targeted by metformin, the drug used most commonly to treat Type 2 diabetes. Clinical diabetologists in the School of Medicine have created the most comprehensive database in Europe describing the morbidity and genetic epidemiology of over 13,000 diabetics in the Dundee area. With major Government investment, they will create the Scottish national web-based diabetes computing system, a register that will have immense research potential.



Scottish Crop Research Institute website: **www.scri.sari.ac.uk/**
ITI Life Sciences website: **www.itilifesciences.com**
BioDundee website: **www.biodundee.co.uk**
MRC-PPU weblink: **www.dundee.ac.uk/lifesciences/mrcppu/**

SET weblink: **www.scottish-enterprise.com/tayside**
Cyclacel website: **www.cyclacel.com**
Upstate website: **www.upstate.com**
CXR Biosciences website: **www.cxrbiosciences.com/content/index.html**

Dundee markets itself as the 'City of Discovery', after the ship *Discovery*, which was built in the Dundee yards and which took Captain Cook on his pioneering voyage to Antarctica. Cook's ship is now a tourist highlight of the city.

Pharmacogenomics and pharmacogenetics is another major strength of the medical school, with a particular emphasis on understanding the basis of individual human variation in the response to drug treatments.

The *Scottish Crop Research Institute* at Dundee, employing about 400, is an international research centre for plant genomics, bioinformatics, pathology, modern plant breeding, genebanks, diagnostics, and viral-vector and gene silencing technology. Facilities range from genetic containment suites to sequencing, genotyping, imaging and mass-spectrometric instrumentation.

Biotechnology in Dundee

With 46 biotech companies (up from 21 in 1998) Dundee is the centre of Scotland's biotech industry. For this reason, the city is home to the newly created *Intermediary Technology Institute (ITI) Life Sciences*. Funding of £150 million ($270 million) from the Scottish Executive will enable it to stimulate further biotechnology development in Scotland over the next decade. *BioDundee* promotes the local life sciences cluster. Its *BioDundee Update* newsletter is read by 14,500 worldwide. *Scottish Enterprise Tayside*, a key partner in the BioDundee initiative, provides assistance to the research institutes and biotech companies in the area to support commercialisation and business development.

Axis Shield, the first University of Dundee spin-off, is listed on the London and Oslo Stock Exchanges, employs over 400 and is a global player in diagnostics. Ten of Dundee's biotech companies, including the three highlighted below, are direct or corporate spin-offs from the university.

Cyclacel, founded in 1996 by Sir David Lane, employs 70 people. Cyclacel designs and develops small molecule drugs that act on key cell cycle regulators to stop uncontrolled cell division in cancer and other diseases involving abnormal cell proliferation.

CYC202, a Cyclin Dependent Kinase inhibitor, is in Phase II trials for breast and lung cancer, while CYC682, a nucleoside analogue, has completed Phase I trials in the USA. Seven other programmes are at earlier stages addressing cancer, diabetes and HIV/AIDS. Cyclacel is the first university spin-off in Britain to raise more than $100 million in private equity.

Upstate, the USA-based biotechnology company, established its first European operations centre in Dundee in 1999, to exploit Dundee's outstanding research base in cell signalling, centred in the *MRC Protein Phosphorylation Unit (MRC-PPU)*.

Upstate is a leader in the supply of high-quality reagents and technologies designed to enhance research into cell signalling and enable drug discovery in an area that promises to revolutionise medical treatments.

Protein kinases, implicated in many disease conditions, comprise their flagship product range and companies developing small molecule inhibitors against these enzymes make extensive use of Upstate's lead profiling service, *KinaseProfiler*. Upstate currently employs 65 staff, is recruiting 20 more, and will take possession of a second custom-built facility in October 2004, to expand its drug discovery platform.

CXR Biosciences, founded in 2001 by Professor Roland Wolf and Dr Cliff Elcombe, now employs 35. Its major objectives are to accelerate drug development by reducing product attrition and to improve the predictability and human relevance of pre-clinical model systems of drug toxicology.

The success of this formula has already led to long-term collaborations with eight major pharmaceutical companies and short-term research projects with 15 others.

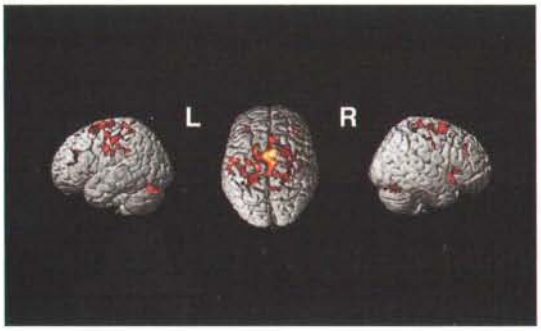
UCL: A leading European biomedical research centre

Professor K M Spyer
VICE-PROVOST (BIOMEDICINE)
AND DEAN OF THE MEDICAL SCHOOL
UCL (University College London)

University College London website: **www.ucl.ac.uk**

Right: **Brain regions in which there is a negative correlation between functional outcome and task-related brain activation during the performance of a dynamic task with the affected hand in chronic stroke patients.** *Institute of Neurology*

Far right: **UCL's central London campus.**



Biomedicine at UCL

UCL is one of Europe's largest centres for biomedical research. It receives the highest level of research funding in the UK for clinical medicine. UCL has associations with a wide range of *National Health Service* hospitals, ranging from major acute trusts *(UCL Hospital, Royal Free)* to specialised trusts *(Moorfields Eye Hospital, Great Ormond Street Hospital for Children)*, and primary care trusts. Its strength resides in the breadth and excellence of its life sciences, their integration into the clinical sciences and the translational research conducted throughout UCL.

Life sciences

Research in UCL's *Faculty of Life Sciences* is concentrated in broad themes that cross traditional departmental boundaries. These include developmental biology, cell and molecular biology, the biophysical and pharmacological properties of ion channels, neuroscience from molecular to cognitive function and population genetics.

There is a focus on evolutionary biology, human performance and cognition, and the development of language. Many of these programmes cross into the *Faculty of Clinical Sciences* and the *Postgraduate Medical Research Institutes*. The embedded *Medical Research Council (MRC) Laboratory of Molecular Cell Biology* is a major contributor to the research profile of the faculty.

Structural molecular biology is a research speciality developed jointly with *Birkbeck College*.

Clinical sciences

UCL's Faculty of Clinical Sciences has major research programmes focused on the clinical roles of its staff.

Cancer Research (CR) is linked to the *North Central London Cancer Network*, which includes major programmes in leukaemia such as the largest bone-marrow transplant programme in Europe – the CR (UK) *Clinical Trials Unit* coordinates much of its translational research.

The faculty has a major interest in cardiovascular research, infection and immunity including HIV, and is characterised by the breadth of these studies, ranging from the laboratory to the clinic with a major emphasis on epidemiology. The importance of primary care is enhanced by the presence of the *MRC Clinical Trials Unit*, and major research programmes include studies on inflammatory diseases including arthritis and amyloidosis, orthopaedics and internal medicine.

New interdisciplinary centres

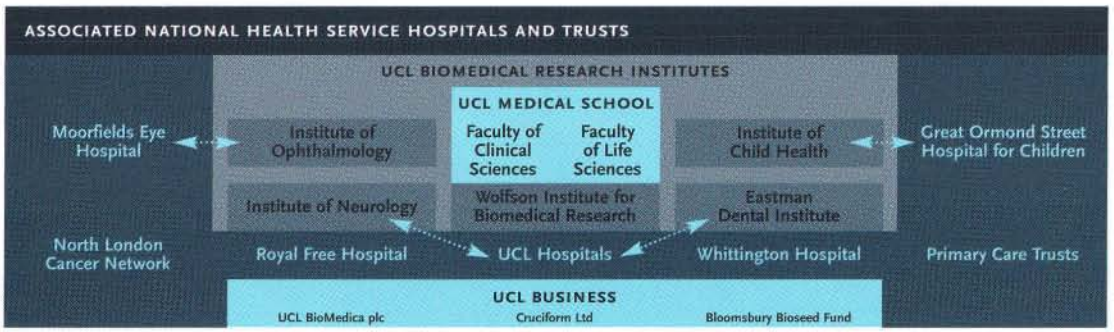
UCL is investing heavily in the interface between biomedical, physical and mathematical sciences through the *London Centre for Nanotechnology* and *CoMPLEX, the Centre for Mathematics and Physics in the Life Sciences and Experimental Biology.*

A major initiative in genetic medicine, involving the Faculties of Clinical Sciences, Life Sciences, *Humanities* and *Laws* is underway. Later this year, a multidisciplinary *Ear Institute* will be opened, as will an *Institute of Women's Health*.

Promoting basic, clinical and translational research

UCL BioMedica website: **www.uclbiomedica.com**
Institute of Child Health website: **www.nichd.nih.gov**
Institute of Neurology website: **www.ion.ucl.ac.uk**
Institute of Ophthalmology website: **www.ucl.ac.uk/ioo**

Wolfson Institute for Biomedical Research (WIBR) website: **www.ucl.ac.uk/wibr**
Eastman Dental Institute website: **www.eastman.ucl.ac.uk**



Research institutes

UCL's *Institute of Ophthalmology*, partnered with Moorfields, has access to the largest population of ophthalmic patients in the western world. It has a multidisciplinary research portfolio that furthers an understanding of the eye and visual system linked with clinical investigations targeted to specific problems in the prevention and treatment of eye disease.

UCL's *Institute of Child Health* is the largest centre in Europe devoted to research into children's health and disease. It is situated in physical and operational continuity with its partner, Great Ormond Street Hospital. UCL's *Institute of Neurology* carries out research in basic neurosciences and, together with its associated specialist hospital, promotes translation of that research into improved patient care and treatment. Its links with the *Institute of Cognitive Neuroscience* and *Gatsby Computational Neuroscience Unit* promote interdisciplinary research.

UCL's *Wolfson Institute for Biomedical Research (WIBR)* operates as an integrated team working to understand the fundamental mechanisms underlying major health problems. It aims to link basic research with the identification and preliminary testing of potential prototypes for new drugs.

Developing intellectual property

UCL BioMedica, a wholly-owned subsidiary of UCL, aims to generate value for UCL through commercial exploitation of bioscience research. The company was created through the merger of *UCL Ventures* and *Freemedic plc*, which between them have generated income in excess of £30 million through licensing and sale of equity in spin-off companies. UCL BioMedica has a team of ten dedicated staff to commercialise bioscience research. It has access to a £4 million seed fund, the *Bloomsbury Bioseed Fund*, dedicated to providing early stage capital to biomedical start-ups. UCL BioMedica is responsible for the creation of *Freemedic Clinical Research*, the *UCL Analgesia Centre* and *UCL Advanced Diagnostics* as wholly-owned subsidiaries to provide clinical research services including clinical trials from Phase I to IV. Together with its associated company, *UCL Cruciform Limited*, which handles intellectual property for the WIBR, a number of spin-off companies have been developed, including *SRPharma*, *PolyMASC* (now merged with *Valentis Inc*), *Ark Therapeutics*, *Inpharmatica*, *Arrow Therapeutics*, *Biovex*, *Xcellsys*, *Ionix*, *Spirogen*, *Stanmore Implants Worldwide* and *Medic to Medic Limited*.

Future perspectives

UCL intends to build on its existing strengths in biomedicine. Major investment in cancer research will focus on the completion of a *Cancer Sciences Institute* in 2006, with a commitment to translational research. This involves an enhanced collaboration with the *Ludwig Institute for Cancer Research*.

Efforts will also be focused on postgraduate training to support biomedical research. This will act both to enhance existing MSc, PhD and MB/PhD courses and to establish new programmes, with a particular emphasis on four-year interdisciplinary PhD programmes.

Bioscience: Expertise and support in the north east of England

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t: +44 191 211 2569

Durham University

Newcastle University

northumbria UNIVERSITY

Teesside University

University of Sunderland

The north east region of England has a well-developed technology based infrastructure focused around the four cities of Durham, Middlesbrough, Newcastle and Sunderland.

All have universities with internationally significant strengths in bioscience. This expertise is embedded in the technical capability of the region's pharmaceutical, speciality chemical and biotechnology companies, who contribute $9 billion to UK GDP and 30% of the UK's pharmaceutical output.

One NorthEast (ONE), the Regional Development Agency created by the UK Government, has invested $300 million (2003 – 2008) in five technology centres of which bioscience is one. ONE is the first point of contact for investment projects, working with a wide range of private and public partnerships to make these projects happen.

A major partner is the *Pharmaceutical and Speciality Cluster (P&S)*, a group of 150 companies, with a further 200 organisations operating in the sector's supply chain. 50 companies with bioscience expertise participate and benefit from this extensive technical and business network which is focused on business development.

P&S, headed by CEO Dr Stan Higgins, acts as the coordinator of the bioscience network, facilitating supply chain development, international business, academic collaboration, technology transfer, best practice and skills development.

Key partners in this are the *Process Industries Centre for Manufacturing Excellence (PICME)* and the *Regional Technology Centre (RTC North)*.

The five universities, *Durham University*, *Newcastle University*, *University of Northumbria*, *Teesside University* and the *University of Sunderland*, are linked through the *North East Science and Industry Council* and work together through the *Universities for the North East (UNIS4NE)*.

Collaborating with industry and ONE they helped to establish the region's five *Centres of Excellence*, two of which work particularly closely with the bioscience sector.

The *Centre of Excellence for Process Innovation (CPI)* and its CEO Nigel Perry develop new processing technologies. The *Centre of Excellence for Life Sciences (CELS)* led by CEO Fred Wright has linked industry, academia and health care providers to drive growth in fields such as cell therapy, stem cells, systems biology, bio-processing and biometrics (including biosensors).

A new national centre, the *Institute for Bioinformatics (IfB)* is also being built in the region. IfB will be market-focused and develop software tools and systems for use in bioinformatics.

The north east of England has a dynamic and increasingly important role to play in international bioscience development and welcomes international cooperation at all levels.

Avecia Rhodia

Avecia website: **www.avecia.com**
Rhodia website: **www.rhodia.com**
Pharmaceutical and Speciality Cluster website: **www.psnorth.com**
Centre for Life Sciences website: **www.celsatlife.com**

Top left: **High-quality manufacturing facilities.**

Top right: **State-of-the-art laboratories.**

Above: **Impressive premises.**

INDUSTRIAL BIOTECHNOLOGY CAPABILITIES IN THE NORTH EAST

- Diagnostics
- Informatics
- Bio-manufacturing
- Bio-catalysis
- Bio-transformations
- Bio-remediation
- Pharmaceutical research
- Microbiological analysis and testing
- Production of antibodies, proteins and peptides

The growth of bioscience companies in the north east of England is impressive. They have been recruiting hard and *Avecia Biologics* have added 200 graduates and PhDs over the last two years.

Recruitment is helped by the concentration of industry expertise in the region, as well as by its cultural renaissance.

Avecia Biotechnology focus on innovative process development and scale-up to fill their *Advanced Biologics Centre*, the largest and newest contract manufacturing facility in Europe.

Key customers include *Celltech Pharmaceuticals*; *Zymogenetics*; *Insmed and Biosynexus*. It is also engaged on a $70 million contract with *Dstl* and *Baxter Healthcare* to make a new anti-anthrax vaccine for the US Government.

Rhodia Pharma Solutions is recognised as being at the cutting-edge of the pharmaceutical industry. It has world leading cGMP manufacturing technologies linked to expertise in bio-transformations and bio-processing. RPS provides process research and development, clinical trial materials, pilot plant facilities and scale manufacture of intermediates and active pharmaceuticals.

Angel Biotechnology delivers cost effective processes for target bio-products by combining special procedures for strain improvement, genetic engineering and fermentation optimisation. Angel offers mammalian cell line construction, manufacture of antibodies and recombinant proteins to cGMP standards.

Xcellsyz, a spin-off from Newcastle University, has developed novel technologies to immortalise human cells while retaining their normal characteristics.

This provides excellent human models for drug testing and greatly accelerates the process of drug discovery. Xcellsyz has supplied muscle cells to *GlaxoSmithKline*, *Novartis* and other pharmaceutical companies.

Creative Gene Technology Limited, a Durham University spin-off is applying genomics and proteomics to develop new solutions for agriculture. Targets include improved oilseed crops and herbicides. Development targets include vegetable oils as lubricants and bio fuels and new more environmentally friendly herbicides.

Nonlinear Dynamics Limited is now a leading worldwide provider of bioinformatics solutions to the life science industry. The company's innovative product portfolio comprises high-quality analysis and data mining tools for 1D and 2D electrophoresis gels and micro arrays, the core technologies of genomics and proteomics.

To contact these and the other bioscience companies in the north east of England visit the Pharmaceutical & Speciality Cluster on **www.psnorth.com**, Centre for Life Sciences on **www.celsatlife.com** or One NorthEast on **www.onenortheast.co.uk**

University of Durham

Molecular biosciences and biotechnology at the University of Durham

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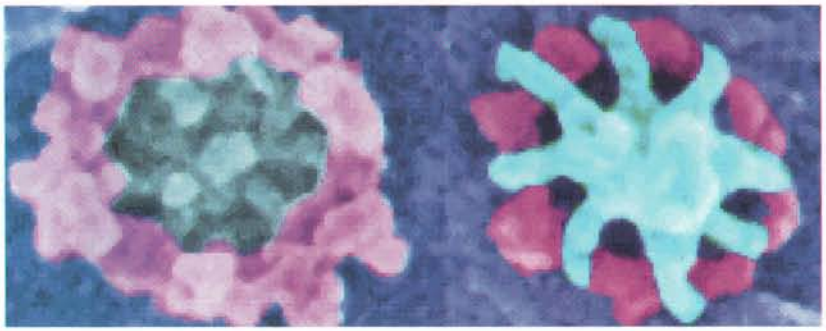
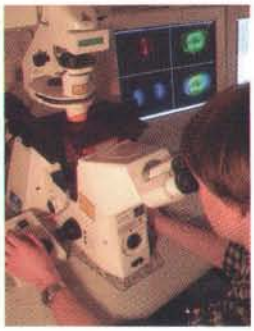
Biological Sciences website: **www.dur.ac.uk/biological.sciences**
Chemistry website: **www.dur.ac.uk/chemistry**

Right: **Field emission SEM to investigate nuclear pore structure.**

Far right: **High-quality research facilities in Durham's Integrative Cell Biology Laboratory.**





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A multidisciplinary approach to fundamental questions in animal and plant cell biology and biochemistry is the key strategy at the *University of Durham*, one of the UK's leading centres in biology. On the basis of its excellence in research and teaching, the school is ranked fourth among UK university biology departments by the 2003 *Times 'Good University Guide'*.

Key elements of Durham's multidisciplinary strategy include:

The Integrative Cell Biology Laboratory (ICBL), a $12 million initiative at the centre of Durham's research in functional genomics. Its name reflects Durham's integrative approach to plant and animal biology. ICBL is underpinned by outstanding facilities in proteomics, transcriptomics, DNA sequencing, imaging and bioinformatics.

The Centre for Infectious Diseases is based in the *Wolfson Research Institute* and houses microbial molecular sciences. It focuses on the structural biology of membrane-bound transporters, tropical disease and genetic recombination.

The Centre for Bioactive Chemistry, a joint initiative with Durham's *Department of Chemistry*, is developing new science at the biology-chemistry interface. It combines studies of signalling mechanisms, structure-function relationships and the development of new molecular probes to study intracellular chemistry.

The new $4 million *Centre for Molecular and Biomolecular Imaging* provides key support to this initiative.

The Centre for Stem Cell Research builds on excellence in skin, hæmatopoietic and neural stem cells, and brings together biologists, chemists and clinicians to address questions of both basic and commercial importance.

Plant molecular sciences is a major strength at Durham. This area of research focuses principally on the plant cytoskeleton, development and cell signalling, protein biochemistry and metabolic regulation.

The *e-Science Research Institute* demonstrates how Durham is establishing new areas of collaboration in systems biology and bioinformatics. Central to this is the interaction between the *School of Biological and Biomedical Sciences* with Durham's *Departments of Mathematics, Computer Science and Physics.*

A major theme here is that of **modelling reality**, drawing on the very high-quality modelling skills of Durham's cosmologists, who run one of the largest academic supercomputers in Europe. Durham is a major partner in the north east region's new *Institute for Bioinformatics*, an industry-facing venture.

Durham bioscience is committed to excellence and welcomes new collaborations.

UNIVERSITY OF NEWCASTLE UPON TYNE

Newcastle University: A culture of enterprise in the biosciences

Newcastle University website: **www.ncl.ac.uk**
For further information, please e-mail: **business@ncl.ac.uk**
or telephone our Business Development Directorate on: **+44 191 2225770**

Right: **Novocastra Laboratories – Britain's most profitable sale of a spin-off company.**

Far right: **Rita Colwell, Director of the US National Science Foundation (1998 – 2004), at Newcastle University to receive her honorary degree.**

Institute of Human Genetics: **www.ncl.ac.uk/ihg**

Institute for Ageing and Health: **www.ncl.ac.uk/iah**

Institute for Nanoscale Science and Technology: **www.ncl.ac.uk/research/institutes/nanoscale.phtml**

Northern Institute for Cancer Research: **www.ncl.ac.uk/nicr**

Earth systems research: **www.ceg.ncl.ac.uk/research/resespc.htm**

When *Newcastle University* awarded an honorary degree to Rita Colwell, the *Director of the US National Science Foundation* in 2002, it cemented a transatlantic relationship which has continued to grow.

American corporations and research institutions play a crucial role in the university's research programme, which is ranked among Britain's top three, with Cambridge and Oxford, in the field of biomedicine.*

The *Institute of Human Genetics* in Newcastle has produced a fully characterised line of human embryonic stem cells and the human feeder cells that can support their growth. Building on research that began in the USA, the Newcastle team is now working towards developing clinical-grade embryonic stem cells, specific to individual patients, which could lead to new treatments for a range of diseases and could even allow complete organs to be grown for transplant.

The *Northern Institute for Cancer Research*, which moved into a new $20 million building this year, is working with *OSI Pharmaceuticals* to develop new drugs to treat prostate cancer and with *Pfizer GRD* on new treatments to increase the potency of chemotherapy and radiotherapy.

The university is developing a *Campus for Ageing and Health* to integrate the UK's largest research group in this field with clinical practitioners. Here, *Amersham* are involved in research to develop and test new methods of diagnosing dementia using the latest imaging techniques.

The university has attracted major public and private investment in biomedical nanotechnology and has a commercialisation arm, *INEX*. New patents include a sensor, developed from micro-gyroscope technology, which can detect tiny molecular interactions and has applications ranging from medical diagnostics to defence.

Other strengths in biomedicine include neuroscience, organ transplantation, diabetes, cell signalling and liver research. Animal, plant and molecular biosciences are also well represented at Newcastle.

Biologists are working with the *US Environmental Protection Agency* to assess the impact of ozone and acid rain pollution on the ecosystems of the Great Smoky Mountains National Park. Civil engineers are collaborating with Pennsylvania State University on 'green technologies' such as an experimental fuel cell to power vehicles, in which bacteria produce hydrogen from waste organic matter.

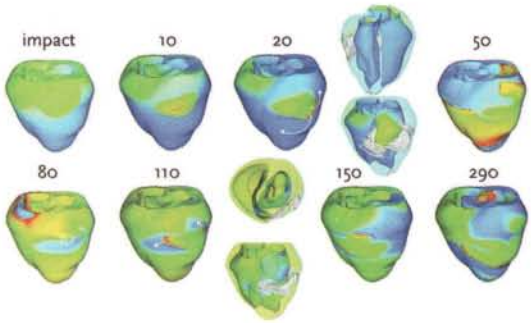
What really sets Newcastle University apart is its dynamic approach to business. A national report on technology transfer last year cited the university as an example of excellence, concluding that its $10.1 million sale of shares in its bioscience spin-off company, *Novocastra Laboratories*, was the most profitable equity sell-off by any UK university.

If you want to find out more about opportunities at one of Britain's most dynamic universities, why not call us?

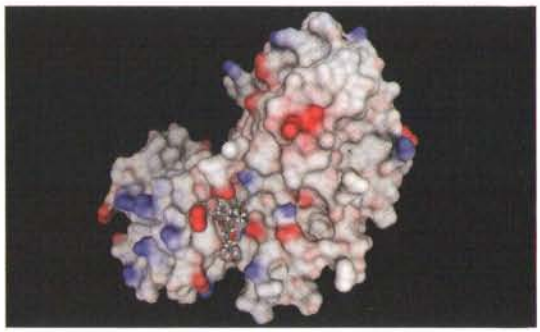
**All biomedical subjects at Newcastle gained the top grades of five or five-star in the most recent Research Assessment Exercise, the UK Government's official measure of research quality in universities.*

From molecular medicine to robot vision, bioscience at Oxford cuts across traditional boundaries

University of Oxford website: **www.ox.ac.uk**



Right: **Denis Noble and colleagues Peter Kohl of Oxford and Natalia Trayanova of Tulane University, New Orleans, have developed a three-dimensional computer model that simulates the impact of drugs or mechanical interventions on the heart. This 'virtual organ' is a feature of the Integrative Biology Project at the Oxford e-Science Centre.** © 2004 *Journal of Molecular Histology*



Far right: **The Screensaver Lifesaver project launched by the Department of Chemistry has recruited more than two million volunteers to use the downtime of their PCs to screen billions of small molecules for potential anticancer activity. CDK-2, one of the target proteins, plays an important role in regulating the cell cycle.** © Karl Harrison

'Oxford University has transferred more IP to the market than perhaps any other university in this country... Oxford has played a significant part in developing what has become one of the most dynamic business regions in the country.'

Visitors dazzled by the city of Oxford's medieval splendour may find such an assessment unexpected. But this testimony to Oxford's entrepreneurship came from an impeccable source: the independent review of business-university collaboration by the former editor of the *Financial Times*, Richard Lambert, published by Britain's Treasury in 2003. Between 1991 and 2000, employment in high-tech manufacturing and services in the Oxford area almost doubled, making Oxford what Lambert called a *'spectacular example'* of a successful business cluster with a research-active university at its heart.

Much of this 'Oxford explosion' has involved the biosciences, underpinned by the discoveries of the university's highly-rated research departments. The *Department of Biochemistry* is one of the largest in Europe. Collaboration between disciplines in institutes such as the *Weatherall Institute of Molecular Medicine*, the *Wellcome Trust Centre for Human Genetics* and the newly-established *Oxford Centre for Gene Function* means that the research community can be fast on its feet in pursuing novel problems.

The new $100 million *Chemistry Research Laboratory* includes chemical and molecular biology as one of its three major research themes, and Oxford's *Department of Physics* is leading a national project on bionanotechnology. The *Diamond* synchrotron light source, a few miles away, is a national facility that will add to the exceptional resources available for studying biomolecules when it comes into operation in 2007.

An international cohort of almost 1,000 doctoral students in the biosciences is the bloodstream of the community. Recent training initiatives include joint PhD programmes with the *National Institutes of Health* and the *Scripps Institute* in San Diego, and a Life Sciences Interface doctoral programme that trains graduates in the physical sciences and mathematics for interdisciplinary work in areas such as bioinformatics.

Oxford has established a fruitful model of science-industry collaboration, with a mix of research grants and contracts, licensing agreements and spin-offs that both provide income and stimulate further innovation. The *Integrative Biology Project* is a collaborative e-Science initiative involving Oxford's *e-Science Centre*, other leading research institutions and *IBM*. The project aims to build a giant computing grid to support the modelling of complex biological systems. A pioneering example of this approach is the *eDiaMoND* project, which uses image analysis software created by Sir Mike Brady of Oxford's *Medical Vision Laboratory* and developed by the spin-off *Mirada Solutions* to improve the accuracy of breast screening programmes.

Oxford's history of successful technology transfer dates from the launch of *Oxford Instruments* in 1959. In the past decade, spin-offs including *Oxford Molecular*, *Oxford Asymmetry* and *Oxford Glycosciences* have

Oxford's model of science-industry collaboration won it the title 'Britain's most entrepreneurial university'

Right: **The Danby and Sherard Buildings offer accommodation for high-tech businesses in the Oxford Science Park.**

BIOSCIENCE IN THE PARK www.oxfordsp.com

Oxford Science Park is home to over 50 high technology companies including many spin-offs from Oxford University.

Oxxon Pharmaccines, launched in 1999 to develop novel therapeutic vaccines to treat diseases such as HIV and cancer, grew out of research on infection and immunity at the Weatherall Institute of Molecular Medicine under Andrew McMichael and Adrian Hill.

Oxford Biosignals, also in the Oxford Science Park, has its origins in research by Lionel Tarassenko in the *Department of Engineering Science*.

His early work on neural networks was supported by *Rolls-Royce* for jet engine monitoring. Now the same technology has found many applications in medical diagnosis and in November last year, Rolls-Royce made a major investment in Oxford Biosignals.

reached stock exchange listing and eventual acquisition by major players in the biosciences sector. Today the university manages the marketing of its intellectual property through its company *Isis Innovation*. Since 1997, Isis has entered into over 160 licensing agreements and launched 40 spin-off companies. Ninety-five per cent of these have attracted private investment, and the current worth of all Oxford spin-offs stands at around $3 billion.

A recent example is *Oxford Biosensors*, which is developing a range of hand-held devices to provide healthcare workers with instant diagnostic results from pinprick blood tests. Founder Allen Hill, of the *Department of Chemistry*, originally pioneered a chemical sensor that made it easy for diabetics to monitor their own blood sugar. That technology was licensed to *MediSense*, a company that now employs around 1,800 people, mostly in the Oxford region.

Oxford University Begbroke Science Park is a new development housing university research labs working with industry, as well as accommodating small-to-medium sized high-tech businesses. One such company is *Oxford Gene Technology*, founded in 1995 by Sir Edwin Southern in the *Department of Biochemistry*. Having given his name to the 'Southern blot' used to detect specific DNA fragments, he went on to develop DNA microarrays to investigate gene function. The company holds patents on this technology and other 'molecular tools', which it licenses to many other companies including *Agilent* and *Amersham*.

These examples illustrate the kind of activities that won Oxford the title of Britain's *'most entrepreneurial university'*. But it's not all about making money. The challenges thrown up by the business world constantly refresh the activity of Oxford's bioscience researchers, whose goal is to understand the molecular basis of life itself.

Bioscience: A thriving sector for Wales

Sponsored by Welsh Assembly Government

Welsh Development Agency website: **www.wda.co.uk**
Wales Trade International website: **www.walestrade.com**

Right: **The Swansea Technium.**

Far right: **Ultrasound output measurement.**

Wales is a dynamic location for a growing bioscience sector with over 230 companies and a number of universities with excellent research facilities. The capital, Cardiff, which is one of the most rapidly expanding cities in Europe, is a two hour drive from London and hosts the renowned *University of Wales College of Medicine* and *Cardiff University*. This academic strength is continued throughout the region and collaboration with this research base is one of the main reasons for the success of Welsh businesses.

Wales has become a prime place to set up bioscience businesses.

Bioscience expertise

In vitro diagnostics. The presence of large companies demonstrates Wales to be a stronghold for development and manufacture in this sector. Coupled with the microtechnology expertise applied to lab-on-a-chip technologies and the digital networks currently being applied to personalised healthcare in Wales, it can confidently be predicted that the region will have an expanding role in this rapidly growing component of healthcare. For example, *Euro/DPC* manufactures and distributes medical immunodiagnostic test kits. The tests are used to diagnose and manage an array of medical conditions such as allergy, anaemia, bone metabolism, cancer, diabetes, infectious diseases, reproductive disorders, substance abuse and thyroid disorders. *Tepnel Biosystems Ltd* is a world leader in meat species testing, in checking for GMO in foodstuffs and in allergen tests such as peanut, milk, gluten and soya, using DNA probes. *Molecular Light Technology* specialises in the production of environmental and human health diagnostic test systems using its proprietary, exquisitely sensitive, chemiluminescence technology.

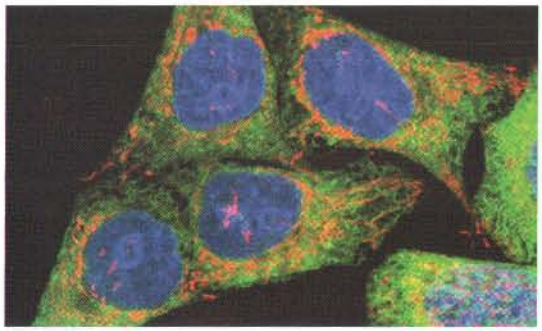
Drug discovery technologies. One of our fastest growing companies, *Amersham Biosciences*, develops leading-edge innovative and enabling systems for genomics, proteomics and drug discovery which are used by the pharmaceutical industry, biotechnology companies and academia worldwide. The Cardiff laboratories employ over 450 people in development and manufacturing.

Clinical trials. Wales boasts a number of companies (eg. *Marix Ltd, Simbec Ltd*) which specialise in early studies of novel therapies in man. The presence of nearby expertise in cancer clinical trials *(Wales Cancer Trials Network)* and in the trialling of new treatments for chronic wounds *(Wound Healing Research Unit)* provides an important part of the critical path for drug development.

Medical devices. The technical skills inherent in Wales have given rise to over 100 medical device companies in addition to those mentioned above. Activities range from product design and development through to specialist manufacturing in dedicated facilities in order to meet the stringent quality regulations.

For example *Biomet Merck* designs and develops orthopædic implants and instruments required for the related surgery and *Huntleigh Diagnostics* produces

WDA: In support of excellence



Single cells are visualised by fluorescent tagging. Interphase tumour cells triple labelled to visualise: nuclei with DRAQ5™(blue); endoplasmic reticulum with GFP-calreticulin (green) and; mitochondria with Mitotracker™ (red). Courtesy of Professor Paul Smith and Dr Rachel Errington, *University of Wales College of Medicine*

ultrasonic diagnostics and Doppler monitors.

Natural products. This is a growing area in Wales. Many small companies work with the technological expertise of *IGER (Institute of Grassland and Environmental Research)* and its state-of-the-art facilities.

Academic excellence

The merger of the *University of Wales College of Medicine* and *Cardiff University*, in August 2004, will further enhance the reputation of Cardiff as a world-class centre for research. These two institutions already boast five of the UK's highest-ranked departments.

The new clinical school at the *University of Wales, Swansea* commences its first graduate intake in September and is already building considerable expertise in cancer research. In addition, a major new teaching programme in protein manufacturing will come on stream in 2004, training graduates to MSc level in all the practical skills required to run GMP facilities.

The *Aber BioCentre* in Aberystwyth combines the skills and expertise of over 450 scientists and represents one of the single largest concentrations of bioscience researchers in Wales.

A recognised world leader in bioscience, the *University of Wales, Bangor's* specialist research centres include the *North West Cancer Research Fund Institute* and the *Centre for Advanced and Renewable Materials.* As an early pioneer of the biological applications of lab-on-a-chip technology, Bangor is a major player in point of care diagnostics.

Over 12,000 new life science graduates enter the workforce every year from Welsh universities, while 13,000 people work in the Welsh bioscience industry and over 50,000 are employed in the *National Health Service* and academic institutions in the region.

Business support

Much business in Wales is facilitated by the *Welsh Development Agency* (WDA) which, together with the *Welsh Assembly Government*, is committed to developing the bioscience sector. The WDA runs a spectrum of initiatives to provide assistance to companies. Various networking groups are facilitated by *MediWales* and *Wales Trade International*. The latter also aids companies in finding partners for international collaboration.

The WDA has set up incubator and grow-on facilities throughout the region many of which include specialist laboratory facilities. The all Wales *'Technium'* programme provides state-of-the-art business innovation for start-up companies delivering a broad spectrum of on-site technical and business support. A major development is projected on the Cardiff Bay waterfront where the *Wales Gene Park* is expected to come together with a new 40,000 sq. ft. commercial bioscience facility in Wales' largest life science park. In addition, a 50-acre site has been set aside for a proposed new biomanufacturing centre close to the new training centre in Swansea University.

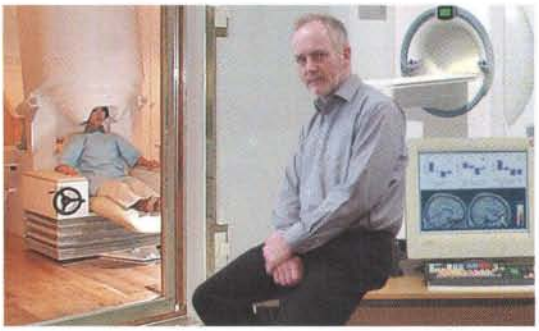
An integrated *'Team Wales'* approach combining the expertise of the WDA, *Welsh Assembly Government*, local authorities, academia and the indigenous companies is adopted so that projects are smoothly and efficiently put into practice. The following pages describe our most prestigious research centres. Should you wish to discuss bioscience in Wales, please do contact the WDA: **www.wda.co.uk**

Cardiff: the powerhouse for bioscience research

University of Cardiff website: **www.cardiff.ac.uk**
University of Wales College of Medicine website: **www.uwcm.ac.uk**
Cardiff Institute for Tissue Engineering and Repair website: **www.citer.co.uk**
Cubric School of Psychology website: **www.cardiff.ac.uk/psych/cubric**

Right: **Sir Martin Evans – Lasker Award winner.**

Far right: **Professor Peter Halligan, Project Director for the Cardiff University Brain and Repair Imaging Centre, pictured with state-of-the-art imaging facilities similar to those to be installed in the new centre.**



Cardiff is the powerhouse of bioscience research in Wales, and its influence is spreading worldwide. Among its wealth of expertise, Cardiff boasts the discoverer of embryonic stem cells, Sir Martin Evans, Professor of Mammalian Genetics and Director of the *School of Biosciences* at *Cardiff University*.

With research collaborators Professor Mario Capecchi of the *University of Utah* and Professor Oliver Smithies of the *University of North Carolina*, Sir Martin successfully used gene therapy to correct the faulty gene that causes cystic fibrosis. This research, which earned the prestigious *Lasker Award*, has a major impact in fields as diverse as cancer, immunology, neurobiology, human genetic disorders and endocrinology.

Cardiff University is one of the UK's leading research-led universities, making a significant and increasing contribution to scientific knowledge. That contribution will be enhanced when it merges in August 2004 with the *University of Wales College of Medicine*, itself an international research leader in a range of life science disciplines.

Collaboration is the key to both institutions' impressive record of achievement, including major international research centres for brain imaging, tissue repair and genetics.

The new Cardiff University *Brain and Repair Imaging Centre*, a direct result of merger, is backed by the UK Government's *Department of Trade and Industry*, and will be among the first in Britain to combine *Functional Magnetic Resonance Imaging (fMRI)* and *Magnetoencephalography (MEG)* solely for research.

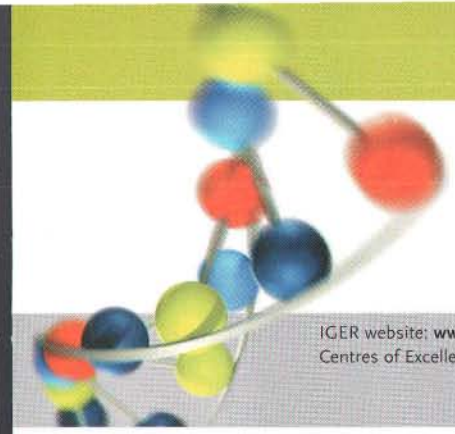
The announcement follows a major commitment to the merged university by the UK's *Medical Research Council* for research into a range of common mental illnesses, which will be led by Professor Mike Owen of the College of Medicine.

The *Cardiff Institute for Tissue Engineering and Repair* uses technological advances to diagnose and treat wide-ranging problems associated with tissue regeneration – such as vision loss, osteoarthritis, sports injuries, chronic wounds and kidney disease.

The institute brings together internationally recognised scientists and academic clinicians from both institutions, working with small and medium-sized businesses to lead research in tissue repair and wound healing.

The *Wales Gene Park*, with funding won in a UK-wide competition, involves both institutions and *NHS Wales* in helping entrepreneurs exploit new technology and genetic testing techniques, and creating opportunities for commercial spin-off companies and job creation. It will lead to the development of a knowledge park dedicated to health-related genetics research.

Other world-class research in biosciences includes major advances in our understanding of memory and emotion; clinical development of polymer-based therapeutics leading to innovative cancer treatment and pioneering work on new treatments for cancer and infections.



IGER: From molecules to landscapes

IGER website: **www.iger.bbsrc.ac.uk**
Centres of Excellence for Technology and Industrial Collaboration website: **www.ceticwales.com**

IGER TECHNOLOGY TRANSFER ACTIVITIES

BUSINESS DEVELOPMENT UNITS	ACTIVITY/TECHNOLOGY	APPLICATION/INDUSTRY SECTOR
Feed evaluation and development	Development and evaluation of high value nutritionals	Animal feed, food
Molecular tools for plant breeding	Microsatellite markers, transposon tools and non-invasive screening	Plant and crop breeding, seeds, agbio
Plant biotechnologies	Plant transformations, tissue culture, hydroponics, metabolite manipulation	Agbio, plant breeding, nutraceuticals, natural product pharmaceuticals
Metabolomics	Bio-analytical tools, data mining and chemometrics for profiling of metabolite content	Natural products, fermentation, diagnostics, crop improvement
Bioproducts from specialist ecological niches	Mining novel biodiversity for genes, enzymes, microbes, plants of value	Animal feed, food, plant science, enzymes, bioremediation
Electronic nose and olfactometry technology	E-nose linked to GC-MS capability for volatiles compound recognition	Novel diagnostics, biosensors, environmental analysis
Bioenergy and non-food/feed applications	Biomass improvement, fermentation, manipulation of plant composition	Energy industry, waste industry, chemicals and manufacturing

Above: **In partnership with University of Wales, Aberystwyth, IGER is the WDA-accredited Centre of Excellence for plant, microbial and animal sciences within Wales, as part of the Aber BioCentre. With an annual turnover of almost US $40 million and a community of over 450 scientists, this centre represents the largest single concentration of bioscience researchers in Wales.**

Institute of Grassland and Environmental Research

Sponsored by the *Biotechnology and Biological Sciences Research Council, IGER* is the largest centre for independent research into grassland-based livestock agriculture and agri-environment relationships in the UK. IGER employs 350 staff, generating US $30 million annually in research income from a variety of public and private sector sources within UK, Europe and internationally.

IGER core R&D programmes

IGER carries out basic, strategic and applied research across three departments: *Plant Genetics and Breeding*, focused on identifying and understanding the genes and molecular basis of traits of interest in key forage crops; *Plant, Animal and Microbial Sciences* which studies how plant feedstocks are converted by the animal and key systems which impact upon these processes; *Soil, Environmental and Ecological Sciences* which studies management of environmental impacts of grassland-based agriculture. This core research is highly integrated including studies on soils, microbes, plants, animals and their interactions, ranging in scale from molecules to landscape and designed to meet the needs of user communities, particularly food, feed and seed industries.

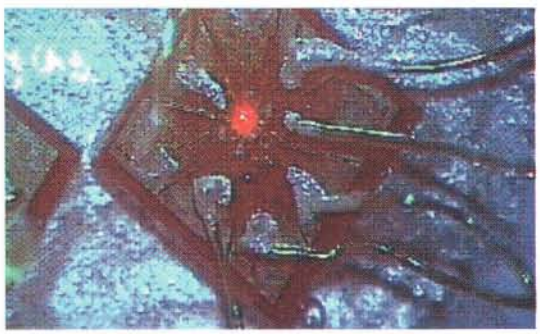
Business and new technology development

IGER has an established technology transfer platform for the creation of new business opportunities. This was done by creating a number of business development units for the optimal exploitation of IPR, expertise and industrial partnerships. The platform drives expansion into traditional industrial sectors eg. animal feed and food (through discovery and development of new nutritional products such as probiotics, anti-microbials, inoculants) and plant breeding (through novel DNA-based and spectroscopic tools for trait analysis). It is also active in leveraging core competencies into other sectors of industry eg. veterinary and human diagnostics (via metabolome studies of animal tissue), drug discovery, nutraceuticals and bioenergy (through manipulation of secondary metabolite production in plants) and biosensors/instrumentation (via high throughput non-biased analytical techniques and chemometrics for chemical profiling of biological samples).

A vital part of the development of innovations from IGER is through global R&D collaborations with academic and industrial partners in both core and novel areas, as the institute expands its range of activity.

Materials, medicine and microsystems: Promoting health and wealth for people and planet

UWB Scientific American weblink: **www.bangor.ac.uk/innovation/sciam**



Right: **Functional additives extracted from agricultural resources.**

Far right: **The 'Optical Biochip' project is a joint programme between Cardiff and Bangor. With the use of microelectrode arrays coupled with specific fluorescent probes and micro-laser arrays, it is possible to manipulate cells and measure their fluorescent responses on a microchip. The lasers used are a mere 10μ in diameter, the size of a single red blood cell.** Courtesy of Dr Huw Summers and Professor Peter Blood, *Cardiff University.*

The *University of Wales, Bangor (UWB)* is a leading academic institution and a recognised world leader in the field of bioscience. A forward-looking and dynamic institution, UWB has an established track record of international collaboration and work with industry.

Research at UWB is conducted across the full spectrum of the biosciences, from the ecological, through the physiological, to the molecular. This is underpinned by a world-class equipment base and integral bioincubator facilities to fast-track commercial opportunities, facilitate industrial links and foster new companies with the active support of the *Wales Spin-out Programme*. Examples of our work include the following:

Natural material technologies

World climate change is driving the need for low carbon technologies, and UWB's international success in the development and application of natural material technologies is able to address this need. A detailed understanding of the composition, extraction and functionalisation, together with the ability to develop prototype products, is essential to the exploitation of bio-derived technologies and UWB has brought all these capabilities under one roof. Fundamental research underpins applied work to generate new materials for applications in drug delivery, wound healing, biodegradable films and functional food additives, whilst research continues to develop industrial, fine chemical and medical applications for bio-derived materials.

Biomedical science

Cancer research. As an early pioneer of the biological applications of lab-on-a-chip technology, UWB regards research in biomedical science a priority, particularly in the field of cancer research. At the *North West Cancer Research Fund Institute* cutting edge studies into the molecular genetics of cancer are complemented by clinical research into the assessment and development of new anti-cancer drugs and the effects of chemotherapy.

Point of care diagnostics. Our understanding of the biochemistry of chronic diseases and cancers, together with fundamental advances in biometrics through the deployment of nanoscale photonic measurement techniques and our in-house expertise in microsystem fabrication enables UWB to play a major role in the development of point of care diagnostics leading to earlier and more accurate diagnosis of medical conditions. Specifically, UWB is collaborating with *Cardiff University* on a prestigious project ($4 million over four years) focusing on the development of optical biochips.

UWB has unique expertise in the development and application of microelectronic technology for the separation and profiling of cells. Applications of dielectrophoresis technology include the profiling and enrichment of stem cells, cancer cells, foetal cells, bacteria and virions for diagnostic and therapeutic applications, as well as the development of rapid cell-based drug discovery assays and biodefence systems.

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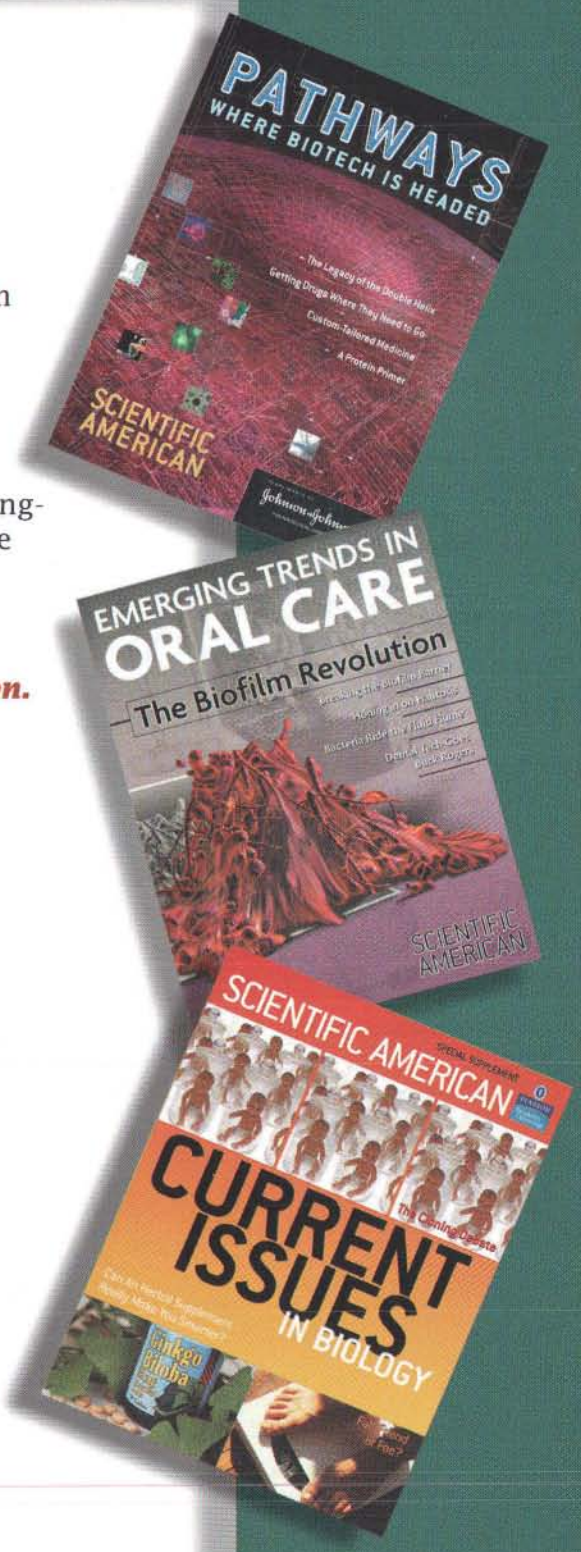

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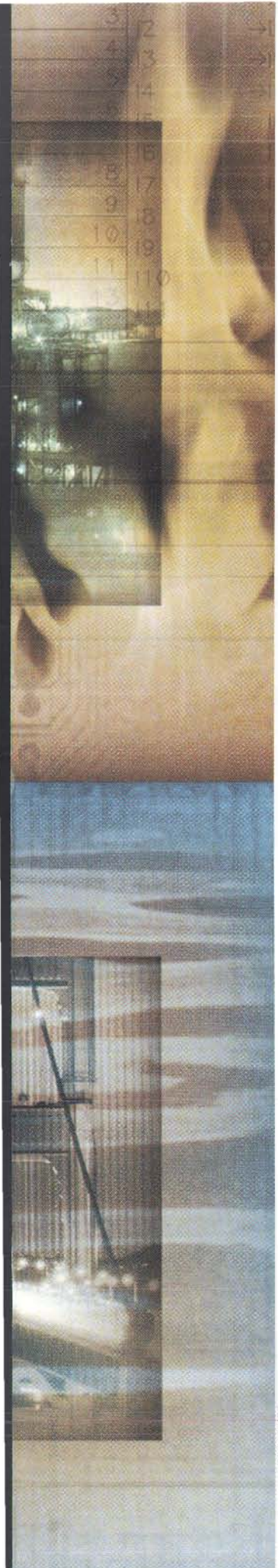


TOM WHITE

Smart Sensors to Network the World

An emerging class of pillbox-size computers, outfitted with sensors and linked together by radios, can form perceptive networks able to monitor a factory, a store—even an ecosystem. Such devices will more intimately connect the cyberworld to the real world

By David E. Culler and Hans Mulder

Today we coddle our computers. They are fragile and expensive, so each typically belongs to an owner who looks after it. When we need to connect many of them into a single system, we hire experts and set aside large amounts of time and money for the job. The sheltered cyberworld of computers still hardly intersects with the real world of birds and trees, ships and bridges.

Where the two worlds do connect, it is often because people have carefully altered objects and methods of work to be computer-friendly. Stores stick bar codes on everything they sell or ship. Warehouse clerks attach radio-frequency identification (RFID) tags to pallets. Tagged goods must then funnel through a few scanners so that the computers can do their accounting.

A new class of microelectronic devices frees us to mix computers much more freely with the objects and places of everyday experience. Our research groups at the University of California at Berkeley and Intel, as well as at start-up firms and other universities, have joined simple computers to radio transceivers and sensors to form small autonomous nodes that we call "motes." Running an operating system known as TinyOS, each mote links up with its neighbors from the moment it is turned on. Although these smart sensors have limited power and processing capabilities, an assembly of hundreds of them can spontaneously organize into a perceptive network that is spread throughout the physical world, able to perform tasks no ordinary computer system could.

These wireless gadgets are affordable and sensitive enough, for example, that dozens have been strapped to redwood limbs to form a new kind of scientific in-

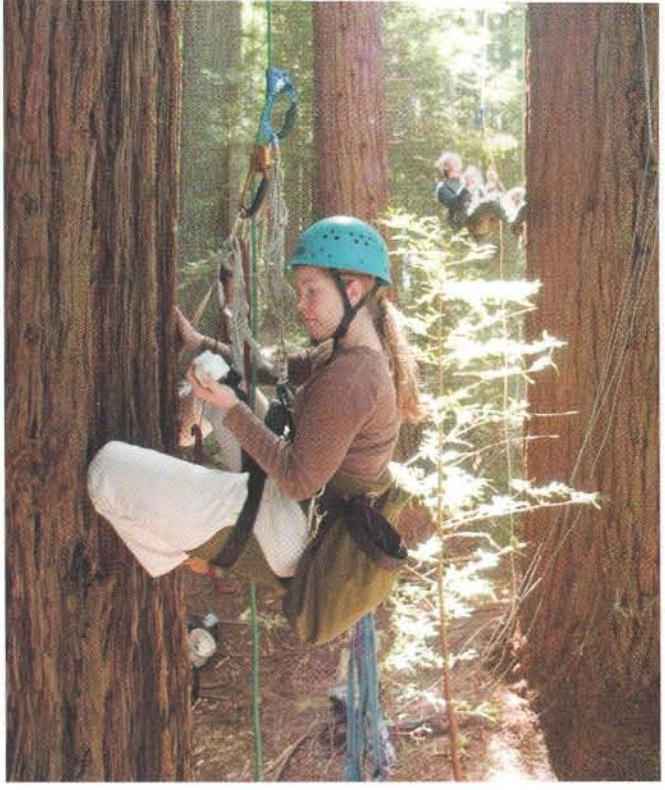
strument—we might dub it a "macroscope"—that records the microclimate around an entire tree in each of several parts of a forest. The battery-powered motes are small enough that this past summer biologists placed 150 of them within and outside the nests of seabirds to help ecologists learn why they brood their eggs where they do. In addition to collecting and processing data, wireless nodes deduce how to route information through their neighbors so that it efficiently reaches an Internet-connected base station. That capability allows Intel to envision placing thousands of such sensor nodes in its manufacturing plants to monitor critical machinery and prevent costly outages.

It is easy to imagine that as the price of motes fall and their capabilities rise along with the rest of semiconductor technology, this novel class of machines will be put to myriad uses: boosting productivity, opening fresh avenues for scientific research, and enabling creative ways to prevent and respond to emergencies, environmental troubles and military engagements. But we do not underestimate the difficult engineering required to realize this potential. A mote is not a miniaturized PC; every aspect of the system, from the way it runs programs to the way it communicates data, must be optimized to conserve power, space and cost. A rule of thumb in designing motes and their networking protocols for long-lived applications is that each device should sleep 99 percent of the time and do its energy-consuming work in the remaining 1 percent.

Computing in the Wild

THE NATURAL WORLD is not computer-friendly. To function outdoors and in industrial settings, computers must be "hardened" with enclosures to protect the electronics from weather, soil, wild animals, and jolts. But sensors must be exposed to the environmental conditions they monitor. Motes have small, inexpensive shells and use redundancy to increase their reliability.

They are designed to be inexpensive enough for deployment in large numbers to gather very detailed information about the environment. Networks of them are dense enough that it is acceptable if some fraction die and smart enough that the overall system can adapt to the loss and keep working. Designing for loss and the uncertainty of the physical world presents new challenges but allows perceptive networks to be economical, portable and unobtrusive.



INSTALLATION in April of dozens of smart sensors throughout redwoods created a network that works as a "macroscope."

While designing successive generations of motes and their networking capability, we have conducted pilot projects to help identify how the technology needs to evolve to be most useful for various applications. Several years ago, for example, we began working with biologists on studies of flocks of about 18,000 petrels that live at sea but fly inland every summer to lay eggs and rear their chicks on Great Duck Island, a small, uninhabited isle off the coast of Maine. The birds nest in underground burrows, which cluster around particular places on the island. Understanding why they choose the brooding spots they do may improve coastal wildlife conservation strategies.

As with many aspects of biology and ecology, what matter are local environmental conditions. A petrel does not dig a burrow where it does because of the average temperature or wind speed on the island but because of how warm or windy it is at that particular spot. Other variables are probably important, too, so biologists would also like to measure humidity levels and the amount of light—both inside each burrow and just outside of it. And investigators want to observe these factors over the nesting season to learn how they correlate with the presence of eggs and the habits of parent birds.

Since 2002 we have been using motes to study the petrels' nesting behavior. The biologists are asking a lot of the technology: to work well for this application (and many others like it), each mote must carry a suite of sensors. In this case, temperature, atmospheric pressure and humidity sensors record microenvironmental conditions, while passive infrared sensors detect the presence of warm birds and eggs. Yet the device must be

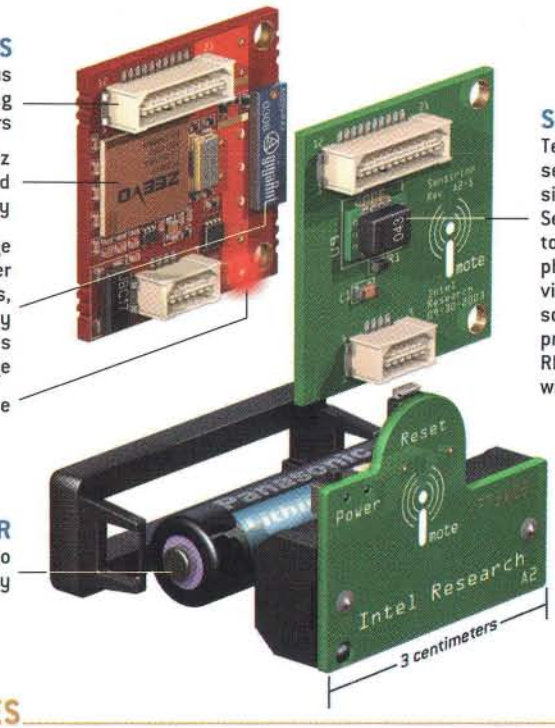
Overview/*Perceptive Networks*

- Thumb-size computers called motes combine microprocessors and memory with radio transceivers, onboard power supplies and a variety of sensors.
- Motes are inexpensive enough to deploy by the thousands in factories, farms or wildernesses. Each mote can collect and analyze sensor readings independently but can also link up with neighboring motes in a meshlike perceptive network.
- Motes are already being manufactured by Crossbow, Intel and others. Early prototype systems have helped biologists study seabird nests and redwood groves. Perceptive networks are also being developed to monitor vibrations of manufacturing equipment, strain on bridges, and people in retirement homes.

CHARLES O'REAR

ANATOMY OF A NEXT-GENERATION MOTE

Smart nodes combine processing and memory capabilities with sensors, wireless communications and a self-contained power supply. A drawing of a prototype iMote produced by Intel Research is shown below. Motes are typically designed in stackable layers so that a processing layer can be connected to a wide variety of sensors and power sources to suit a range of applications.



PROCESSING AND COMMUNICATIONS

Standard connectors allow various combinations of processing, sensing and power layers

Integrated microchip contains a 12-megahertz processor, 64 kilobytes of RAM and 512 kilobytes of flash memory

Radio antenna is designed to exchange data at 200 to 600 kilobits per second over a range of up to 30 meters, using a 2.4-gigahertz frequency and the Bluetooth protocol, which has posed an interesting technical challenge

Multicolor LED indicates status of iMote

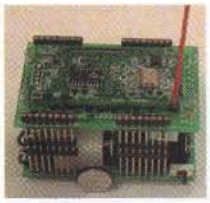
SENSING

Temperature and humidity sensors are integrated on a single silicon microchip. Sensor boards are available to measure many phenomena—including vibration, acceleration, sound, and atmospheric pressure—as well as to read RFID tags and to interact with other wireless systems

POWER

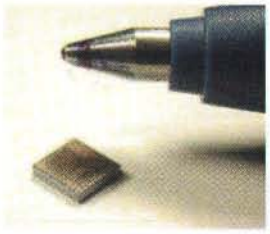
Lithium-ion battery pack stores two to three watt-hours of electrical energy

MOTES OF ALL SHAPES AND SIZES



Mica mote, shown atop a Robomote made at the University of Southern California, is in use in some 500 research projects. Using motes that control actuators, perceptive networks can operate machinery, regulate indoor environments, and change the position of the sensors in the system.

Mica2Dot, a quarter-size version of the Mica made by Crossbow, incorporates four kilobytes for data, 128 kilobytes for programs and a 900-megahertz radio transceiver. Sensor layers connect to the processing board using pins on the circumference of the device. These motes formed the redwood- and seabird-monitoring networks.



Smart Dust prototype, developed at Berkeley, performs many TinyOS functions in hardware rather than in software. Thanks to its ultraefficient radio and analog-to-digital converter, the five-square-millimeter device would be able to run on energy harvested from ambient light or vibration.

GRIFF WASON [*illustration*]; COURTESY OF GAURAV S. SUKHATME *U.S.C. Embedded Systems Laboratory* [*Robomote*]; COURTESY OF CROSSBOW TECHNOLOGY [*Mica2Dot*]; JASON HILL [*Smart Dust*]

no more than a few centimeters in size so that it does not disturb the bird and its chicks. Clearly, it must be wireless, because it is not feasible to string power and network cables over acres of nesting grounds. So the device must carry its own energy, enough to power the electronics for the annual nesting season. And it must keep running and communicating its information through other nodes in the network without any human contact.

Many of the system's design constraints boil down to power. A single bulb on a strand of Christmas tree lights consumes about half a watt. Whether they use batteries, solar cells or gadgets that harvest energy from vibrations, as self-winding watches do, motes must operate on $1/10{,}000$ of this power on average.

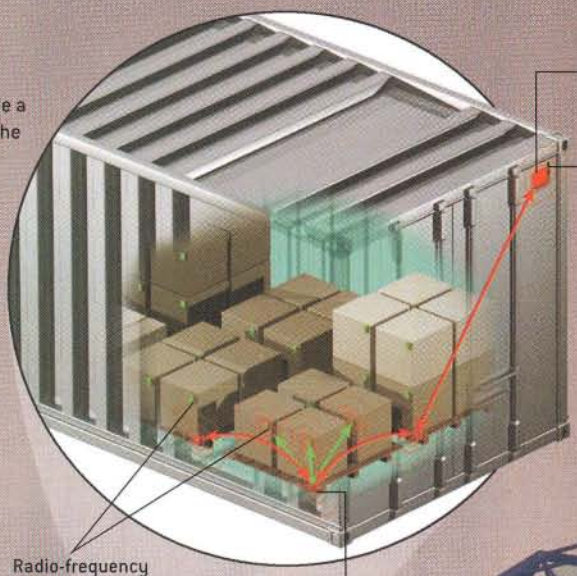
A solar cell that is one square centimeter in size generates about 10 milliwatts (thousandths of a watt) in full sunlight; solar cells work poorly indoors and not at all inside burrows. A typical coin-size battery stores about three watt-hours of electrical energy. Microcontrollers generally burn about 10 milliwatts of power; low-power radios burn about 20 milliwatts. Many useful sensors consume similar amounts of power. Even running at a mere 30 milliwatts, however, such a battery will last for less than five days.

That is why motes spend about 99 percent of their lives "sleeping" in a standby mode that drops the power consumption to a few millionths of a watt. Several times each second, the device flicks on its radio to check for incoming messages, but if there are none, the radio is shut off within milliseconds. Similarly, the sensors usually take their readings of the temperature, light level and so on only once every few minutes.

A SELF-ORGANIZING SMART SENSOR NETWORK

A perceptive network of smart, wireless sensors called motes could help customs officials prevent weapons or contraband from being smuggled in through ports. Each cargo container might hold numerous motes able to self-organize into wireless networks. Those on pallets inside each container could link up with a node on the container wall, and that device could in turn share data with motes on all the other containers on the ship in an efficient, treelike network. The port official's laptop

1 A mote on each pallet could use a built-in RFID reader to record the identity and origin of each box it carried (*green arrows*). A node mounted on the wall of the container could aggregate data from the pallets inside (*red arrows*) and use its own sensors to note whether the container became too hot, cold or humid; whether it was dropped or bumped; or whether material was, suspiciously, added or removed during the voyage.



3 A program called TinyDB ("DB" for database), created by Intel Berkeley and U. C. Berkeley, would run on each mote and effectively hide the complexity of the network from the user. For example, the customs official might request that the network report each container's identification number, its origin and destination, and the dates it was loaded and last opened. Those opened en route could be flagged. A shipping agent might use the system differently. He could query the network to identify any cargo that was exposed to high temperatures or humidity, potentially damaging the goods. He might also use motes on cranes and other motors to check for wear or fatigue.

ID	ORIGIN	DEST.	LOADED	OPENED
2034	SYD	SFO	02-03-04	02-01-04
2035				03
2036				04
2037				03
2038				04
2039				03
2040				03
2041				04
2042				04
2043				03
2044				04
2045	SYD	LAX	01-09-04	12-31-03
2046	SNG	LAX	02-03-04	04-01-04
2047	TYO	LAX	03-11-04	10-21-03

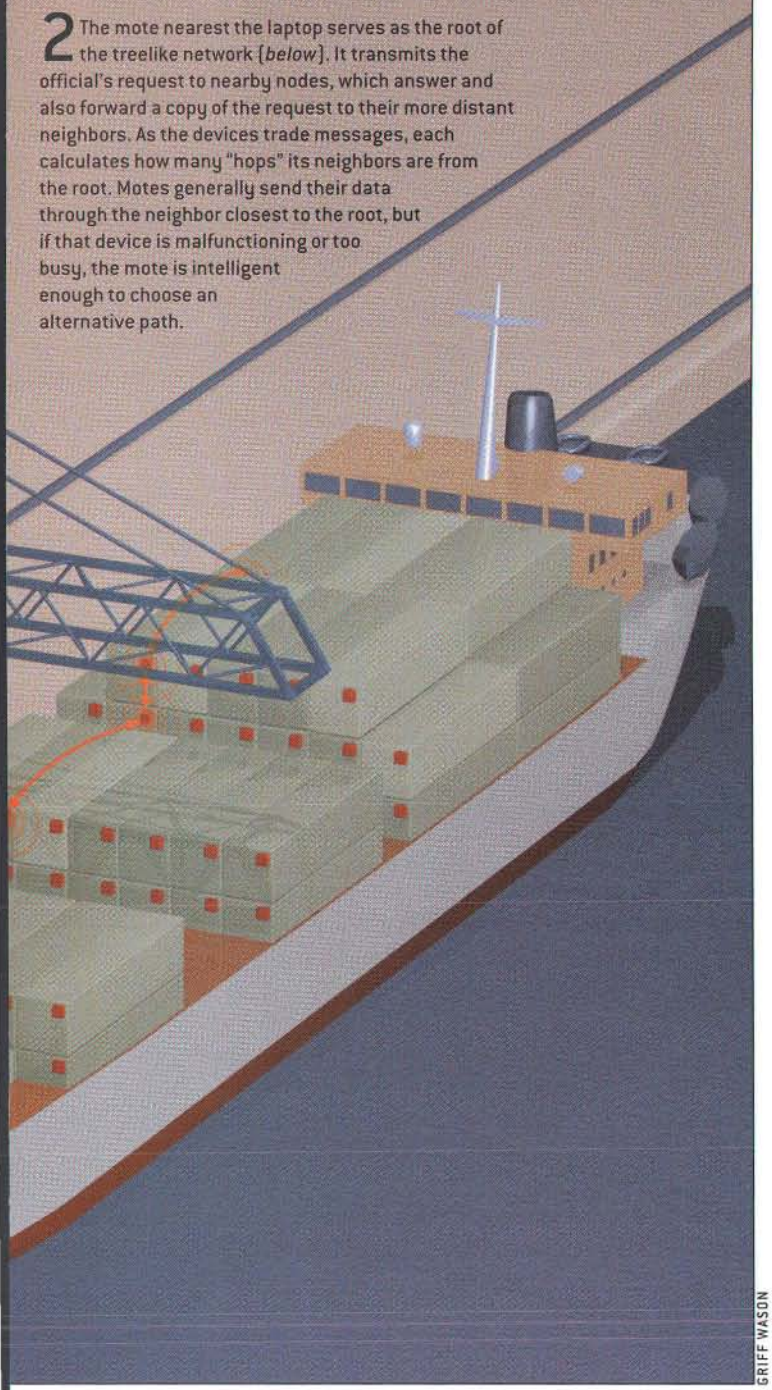
ALERT!

Container 2046 opened en route

OK

computer thus needs to communicate with only one of the containers to retrieve a summary of all cargo on the ship and more detailed sensor readings for any anomalous containers that might warrant manual inspection.

2 The mote nearest the laptop serves as the root of the treelike network (*below*). It transmits the official's request to nearby nodes, which answer and also forward a copy of the request to their more distant neighbors. As the devices trade messages, each calculates how many "hops" its neighbors are from the root. Motes generally send their data through the neighbor closest to the root, but if that device is malfunctioning or too busy, the mote is intelligent enough to choose an alternative path.



GRIFF WASON

Most techniques for saving energy exploit the intelligence within the device to perform local processing and to turn off unneeded resources. We often use a simple, low-power sensor to turn on others in response to a preprogrammed stimulus. When a bird enters a nest, for instance, the temperature rises quickly. A heat-sensitive circuit could take readings once a minute and trigger a camera or other power-hungry sensors on the mote to start recording whenever the burrow warms rapidly.

The onboard processor offers other ways to save power. Communicating one bit of data through the radio transceiver costs as much energy as executing roughly 1,000 processor instructions. The mote can conserve power by storing and aggregating sensor readings, rather than sending them out immediately. The processor can also compress information before it is sent and can summarize the sensor logs with an average or the high and low values if the details are not crucial. Nodes may swap sensor data with one another, identify important observations and then send simplified descriptions out to the user. There is no way around certain network-protocol conversations between nodes, but these messages can be held until there are sensor measurements to transmit and then stuffed into the same "envelopes" as those packets of data.

The project on Great Duck Island successfully tested these and other ideas for making the most of wireless sensor networks on this scale. And in the 2002 breeding season alone, the macroscope there was able to take more than a million measurements, adding far more detail to biologists' picture of a key scene in the life cycle of petrels. Just as important, the technology allowed scientists to observe the birds without alarming them by a human presence.

Networking out on a Limb

COMPARED WITH a handheld PDA, an individual mote is a computational weakling [*see box on page 55*]. Each mote has a microcontroller that can handle four million to 10 million instructions a second, whereas a palmtop can whip through about 400 million a second. But unlike PDAs, motes can join forces in ad hoc networks to form a system that has greater computational power than its parts.

In April we assembled such a system by strapping 120 plastic-encased motes to the trunk and limbs of redwoods at a grove near Sonoma in northern California. The goal is to build a detailed picture of how the microclimate enveloping such trees changes and how the trees shape the local environment through their shade, respiration and water transport. For this project,

THE AUTHORS

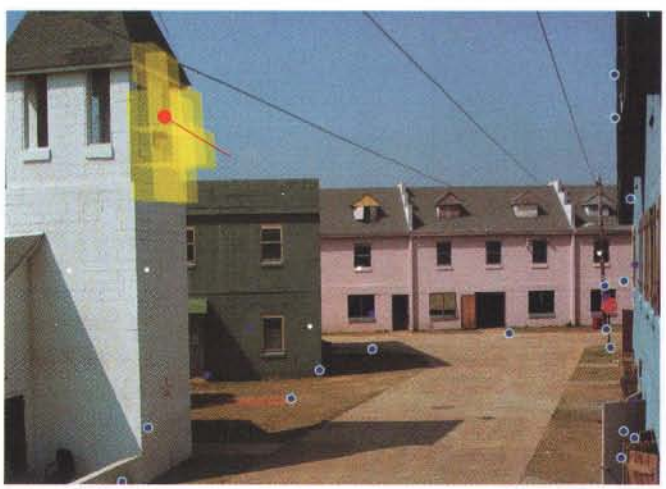
DAVID E. CULLER and *HANS MULDER* have collaborated for many years on wireless sensor node research. Culler is professor of computer science at the University of California, Berkeley, and was the founding director of Intel Research Berkeley. For the past decade his research has focused on ways to combine large numbers of computers to work in a highly coordinated fashion. Hans Mulder is associate director of Intel Research and director of the Intel Research network of university labs. He initiates and drives research on ubiquitous computing and distributed systems.

cost determines the density of measurement, and power determines the lifetime. The network will run for several weeks on AA-size lithium batteries. The larger challenges in this case are collecting data from devices that are so high up that they are out of radio contact with the ground and reprogramming the motes as needed to test different hypotheses about the interaction between the forest and the environment.

The low-power, silicon microchip radios in the devices can transmit and receive data about as fast as a dial-up modem, but their range is limited to less than 30 meters—sometimes much less. In a forest, wet wood and needles attenuate the signals. A mote stuck to a tree trunk often cannot communicate directly with a neighbor on the other side of the trunk just a meter or two away. To cope with these limitations, a mote might beam its sensor readings to a mote on a higher limb. From that node, the data packets could travel to motes in the treetop and then continue hopping from one device to the next down the far side of the tree, over to other trees on the edge of the grove, and finally out for storage and analysis on a more powerful computer. The sensor-network macroscope in Sonoma is designed to relay its redwood measurements to a PDA-like cellular device on the ground and then through the Internet to a server in Berkeley, 70 kilometers away.

When a deployment involves hundreds of motes, it is not practical to set up such multihop networks by configuring each device individually, as is done in a typical office or cellular network. For many applications of perceptive networks—monitoring equipment, raw materials, and products in a factory or on a farm, for example—the arrangement of motes will be constantly changing. So the motes self-organize into networks. Special algorithms running in each sensor node determine how many hops it is from the server and which of its neighbors offers the most efficient path to that collection point at any given moment [*see box on preceding two pages*].

Mote-to-mote communications are coordinated by an operating system on each mote as well as by an application program that can run in pieces, with different pieces on different nodes in the network. Standard operating systems, such as Windows or Unix, are much too large and processor-intensive for these tiny devices. That is why Culler's group at Berkeley created TinyOS, an extremely compact, network-centric operating system that is now "open source" and maintained by a community of programmers using it in their own work.



GUNSHOT LOCATION and trajectory (*red dot* and *line*) were triangulated within seconds by a network of microphone-equipped motes (*blue dots*). In tests at Fort Benning, Ga., the system pinpointed rifle shots even when some motes (*white dots*) had no clear line of sight to the muzzle blast.

TinyOS is stingy with power; it forces mote programs to shut down except when certain events occur that warrant action. The operating system is also highly modular. If a program needs only certain functions from TinyOS, the nonessential parts of the operating system are automatically removed from the mote. This modular approach ensures that the program code fills as little memory as possible, leaving more room for sensor data. Modules also enhance the robustness of the devices by limiting how the distinct parts of the software interact.

Commanding a Computational Army

PERHAPS THE MOST challenging long-term question raised by perceptive networks is how we can most efficiently and reliably program the thousands of smart nodes that may coexist in a system. This scale is no idle conjecture: Intel has begun installing prototype nodes called iMotes on pumps and other machinery at its Jones Farm fabrication plant in Hillsboro, Ore. About 4,000 places in such a facility hold equipment that should be monitored for signs of wear and failure—so many locations that currently engineers can check only selected pieces every one to three months. That is not frequent enough. Not long ago a device failure occurred between two vibration inspections at an Intel plant, causing a costly interruption of operations. An entire system of 4,000 iMotes could be created now for well under $1 million that could provide hourly updates on the health of the plant's infrastructure, with no need for roving engineers. But we have had to think carefully about how to program and debug the network so that it remains manageable as it grows to include thousands of sensor nodes.

Because of the tight constraints on power use and processor speed, a perceptive network functions differently from the Internet and office LANs, where computers have individual names and addresses and most messages are sent from one machine to a specific recipient machine. In sensor networks, one node generally broadcasts messages to many, with the intended recipients identified by attributes such as their physical location or sensor value range.

Recently a team at Intel and Berkeley created software called TinyDB that makes a perceptive network system function much like a database. A user can "query" all the smart nodes at once with a request for, say, any vibrations between 40 and 120 hertz stronger than a certain level. The request enters the network at its "root" node, which forwards copies to its neighbors and so on until all sensors have received the command.

Motes that lack vibration sensors may ignore the message; others may turn on their sensors if they have been sleeping; still others may run a series of calculations on the data logged in their memories, extract readings that meet the requested crite-

AKOS LEDECZI *Vanderbilt University*

PROTOTYPES OF PERCEPTIVE NETWORKS

PURPOSE	SENSORS	NODES	ORGANIZATION
Observes weather and nesting behaviors of seabirds on Great Duck Island, Me.	Temperature, humidity, infrared	150	Berkeley, Intel
Analyzes activity of residents in elder care facilities in Portland, Ore., and Las Vegas	Motion, pressure, infrared	130	Intel
Antitank mines communicate and reposition themselves to close gaps in a mine field	Location, orientation, acceleration	96	DARPA
Collects readings on microclimates surrounding redwood trees	Temperature, humidity, light, atmospheric pressure	80	Berkeley, Intel
Monitors the performance of pump and scrubber motors in a microchip factory	Vibration and RPM	70	Berkeley, Intel
Maps growth conditions and susceptibility to fungal infections in a vineyard	Temperature	65	Intel
Listens for gunshots and then triangulates shooter position	Sound, shock wave, location	45	DARPA, Vanderbilt
Records microclimates within James San Jacinto Mountains Reserve, Calif.	Temperature, humidity, rainfall, light, wind	30	U.C.L.A.
Monitors movement of Golden Gate Bridge	Vibration and acceleration	Under design	Berkeley

ria, and pass that information back to the root mote for collection. All the user sees is a spreadsheetlike list of the relevant measurements and locations. Software running on a high-powered server could then perform a wider analysis of the trends to determine which machines require maintenance.

In the redwoods, biologists are most interested in the dramatic temperature and humidity fronts that move up and down the tree every day, creating powerful gradients that may drive the flow of nutrients. To track these fronts, motes pool their data and search for spatial patterns. As scientists and engineers learn from their observations through the macroscope, they periodically change the tasks the network performs.

To replace the software on motes with updated versions, we have drawn on lessons from Internet viruses and worms. A new program is packaged in a special form and delivered to the root mote, which installs it and "infects" its neighbors with the package. The upgrade makes its way through the network like an epidemic, but it does so in a more controlled fashion that avoids redundant communications and adapts to the way that the motes are scattered in space.

This reprogramming model immediately suggests one of the harder problems in sensor network design: how to secure them against hackers, viruses and eavesdroppers. TinyOS has built-in algorithms that can authenticate the identity of motes. But for the system to work well, keys must be distributed to a large number of small nodes in reliable and uncomplicated ways. Malefactors can attack perceptive networks using strategies that are quite different from what is generally seen on the Internet. One promising way to defend the networks is to treat the effects of an attack as essentially another form of noisy sensor data, so the perceptive network as a whole will still function even if a small fraction of nodes has been compromised. But as with all forms of computer security, the protection of mote systems will be a constant battle of wits.

As we gain experience with this new kind of tool, we find that it fails in unfamiliar ways. A sensor network is unlikely to crash outright, but as some nodes die and others generate noisy or corrupt data, the measurements of the overall system may become biased or inconsistent. We and other computer scientists are working on techniques to judge the health of a perceptive network by perturbing the system in a controlled way and observing how the sensors respond.

Over the next decade or so, wireless sensor nodes and perceptive networks will probably evolve into a much less distinct and less visible form. Devices will gradually migrate out of their little boxes and will instead be incorporated directly into various materials and objects. Many will draw energy directly from the environment in which they operate. To the extent that these kinds of computers infiltrate homes, workplaces, farms, transportation terminals and shopping sites and are able to sense the presence, motion and even physiological states of individuals, they will raise substantial privacy concerns. Indeed, a discussion about such technology has already begun over the use of passive RFID tags [see "RFID: A Key to Automating Everything," by Roy Want; SCIENTIFIC AMERICAN, January]. Privacy issues are straightforward for many valuable applications—such as monitoring vibrations in pumps, fatigue in beams or microclimate in forests—but in other domains a careful balance must be struck to ensure that the technology properly empowers the individual.

With appropriate debate, these matters will surely be surmounted—mote technology is too useful to ignore. By connecting us to the physical world in ways not previously possible, it promises to advance scientific pursuits and the businesses of manufacturing, agriculture, construction and transportation. SA

MORE TO EXPLORE

Mica: A Wireless Platform for Deeply Embedded Networks. Jason Hill and David Culler in *IEEE Micro*, Vol. 22, No. 6, pages 12–24; November/December 2002.

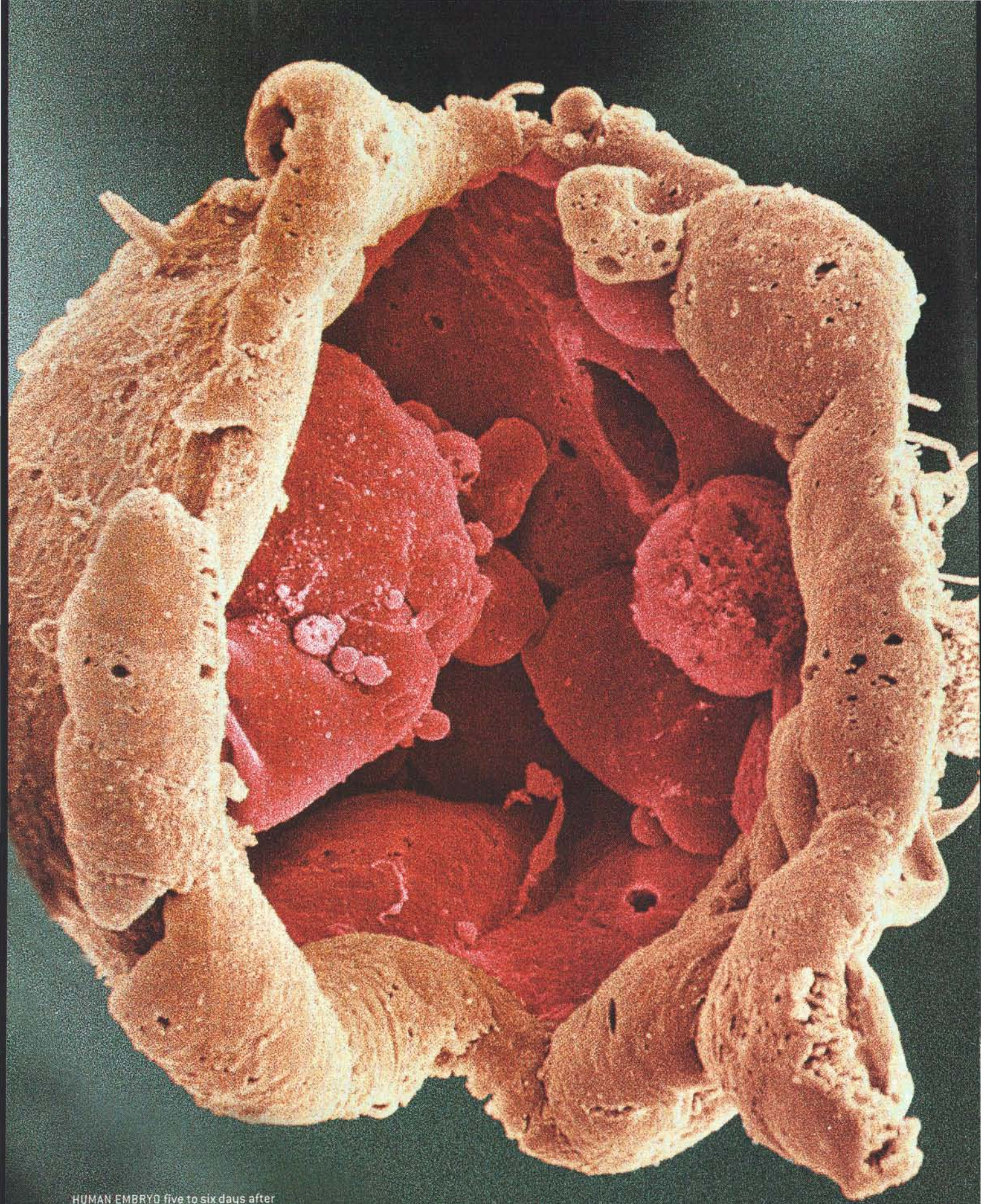
Query Processing in Sensor Networks. Johannes Gehrke and Samuel Madden in *Pervasive Computing*, Vol. 3, No. 1, pages 46–55; January 2004.

The Emergence of Networking Abstractions and Techniques in TinyOS. David Culler et al. in *Proceedings of the First USENIX/ACM Symposium on Networked Systems Design and Implementation*. USENIX, 2004.

Great Duck Island monitoring network: **http://greatduckisland.net**

TinyOS: **www.tinyos.net**

U.C.L.A. Center for Embedded Networked Sensing: **http://cens.ucla.edu**



HUMAN EMBRYO five to six days after fertilization, called a blastocyst, is opened to retrieve the inner cell mass (*red bulge*) that produces embryonic stem cells.

The Stem Cell Challenge

What hurdles stand between the promise of human stem cell therapies and real treatments in the clinic?

By Robert Lanza and Nadia Rosenthal

Stem cells raise the prospect of regenerating failing body parts and curing diseases that have so far defied drug-based treatment. Patients are buoyed by reports of the cells' near-miraculous properties, but many of the most publicized scientific studies have subsequently been refuted, and other data have been distorted in debates over the propriety of deriving some of these cells from human embryos.

Provocative and conflicting claims have left the public (and most scientists) confused as to whether stem cell treatments are even medically feasible. If legal and funding restrictions in the U.S. and other countries were lifted immediately, could doctors start treating patients with stem cells the next day? Probably not. Many technical obstacles must be overcome and unanswered questions resolved before stem cells can safely fulfill their promise.

For instance, just identifying a true stem cell can be tricky. For scientists to be able to share results and gauge the success of techniques for controlling stem cell behavior, we must first know that the cells we are studying actually possess the ability to serve as the source, or "stem," of a variety of cell types while themselves remaining in a generic state of potential. But for all the intensive scrutiny of stem cells, they cannot be distinguished by appearance. They are defined by their behavior.

Most versatile are embryonic stem (ES) cells, first isolated in mice more than 20 years ago. ES cells come from the portion of a very early-stage embryo that would normally go on to form three distinctive germ layers within a later embryo [*see illustration on page 63*] and ultimately all the different tissues of the body. ES cells retain this potential ability to produce any cell type in the body, making them pluripotent.

Most of the existing human ES cell lines in the world were derived from unused embryos created for couples seeking in vitro fertilization (IVF). Researchers working with these cells have found that they usually recover after freezing and thawing and can differentiate into assorted cell types in a culture dish. But it is becoming clear that not all human ES cell lines are the same.

YORGOS NIKAS *Wellcome Photo Library*

Seeking Stemness

SOME LINES WILL differentiate into only certain cell types; others grow sluggishly in culture. To ensure that these cells are pluripotent before using them in research, two possible tests, already common in nonhuman ES cell studies, have been proposed by a group of American and Canadian biologists hoping to set standards for experimentation with human ES cells. One would involve injecting the ES cells into an animal's body tissue. If they form a teratoma—a distinctive tumor containing cell types from all three embryonic layers—their pluripotency is proved. Another way to test putative ES cells is to mark them, then inject them into a developing animal embryo. When the animal is born, if the marked cells turn up in all its tissues, the cell line is deemed pluripotent. But testing human embryonic stem cells in this manner would create a chimeric animal with human DNA throughout its body, a prospect many find ethically troubling. What is more, passing the latter test does not always guarantee that the cells will differentiate in the lab.

The need to find more reliable markers that distinguish truly pluripotent ES cells is driving widespread attempts to catalogue the genes that are turned on or off at various times in cultured ES cells. Having such a gene expression profile would not only provide a way of identifying pluripotent ES cells, it would also offer tremendous insight into the properties that confer their "stemness." Unfortunately, to date, gene expression profiles of ES cells have yielded conflicting results, and the search for a clear ES cell signature continues.

Of course, the goal of stem cell research is to replace or regenerate failing body parts, such as pancreatic insulin-producing cells in diabetics or dopamine-producing neurons in people with Parkinson's disease. But techniques for coaxing ES cells to differentiate into desired cell types are far from perfected.

Left to their own devices in a culture dish, ES cells will spontaneously differentiate into a hodgepodge of tissue types. With timed administration of chemicals, we can often direct them to become one cell type or another. But they seem to prefer to become certain tissues—readily proliferating into patches of beating heart cells, for example—whereas other tissues are far more difficult to derive.

Putting Cells to Work

BECAUSE WE STILL do not understand the signals that normally instruct these cells to choose a particular pathway during embryonic development, many researchers are studying the natural embryonic "niche" to understand possible environmental cues. Other scientists are trying to profile embryonic cells' gene expression patterns as they differentiate in order to find genes that could be turned on or off to direct the cells toward a particular tissue type.

But deriving what appear to be cells of the desired kind is just half the battle. ES cells will easily produce dishes full of neurons, for instance, but these are only useful if they can be placed in a living brain, make connections and "talk" with surrounding neurons. In 2001 stem cell researchers thought they had a major breakthrough when Ronald McKay of the National Institutes of Health reported having generated insulin-producing cells—a coveted goal in stem cell research—from mouse ES cells. Last year, though, Douglas A. Melton of Harvard University reproduced McKay's experiment and found that the cells had absorbed insulin from their culture medium rather than producing it themselves. Discovering markers to identify truly functional cells is another urgent task for the stem cell research community.

It would be ideal if we could simply inject ES cells into the part of the body we wish to regenerate and let them take their cues from the surrounding environment. ES cells' pluripotency, however, makes this far too dangerous an approach for human therapy. The cells might form a teratoma or could differentiate into an undesirable tissue type, or both. In animal experiments, teratomas containing fully formed teeth have been reported.

Rather than risk creating a tumor or a tooth in a patient's brain or heart with direct ES cell injections or struggling to produce specific functional tissues, many ES cell researchers are now striving for a middle ground. By coaxing ES cells into a more stable, yet still flexible, progenitor-cell stage before administering them, we can avoid uncontrolled differentiation while still taking advantage of environmental cues to generate the desired cell types.

Even though these progenitor cells can take to their environment and initiate the generation of new tissue, they would still be subject to attack by the patient's own body. ES cells and their derivatives carry the same likelihood of immune rejection as a transplanted organ because, like all cells, they carry the surface proteins, or antigens, by which the immune system recognizes invaders. Hundreds of combinations of different types of antigens are possible, meaning that hundreds of thousands of ES cell lines might be needed to establish a bank of cells with immune matches for most potential patients. Creating that many lines could require millions of discarded embryos from IVF clinics.

Some researchers have speculated that such an extensive bank might not be necessary, that patients can be desensitized to ES cell derivatives or that the

Overview/*Stem Cell Prospects*

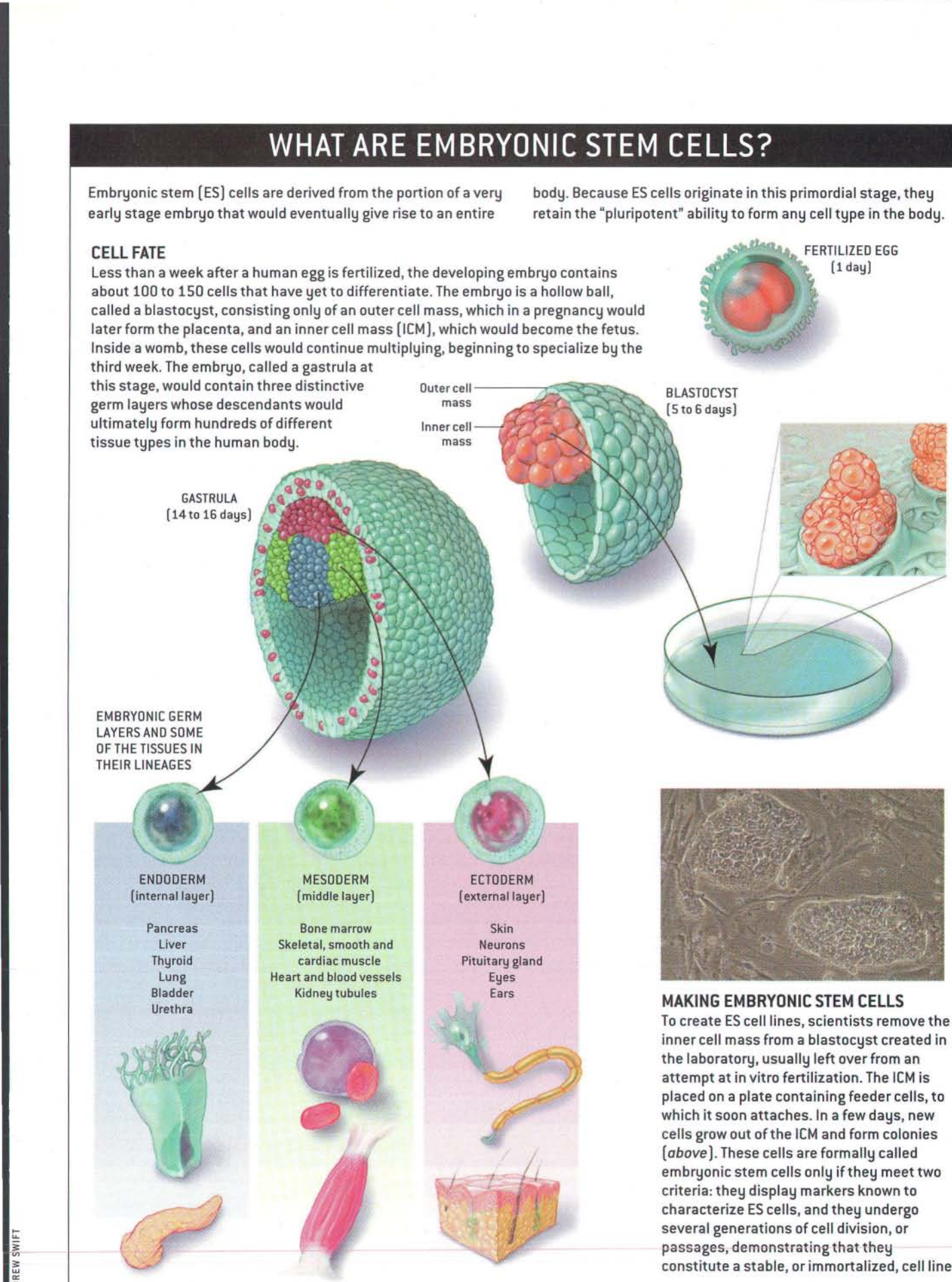
- The possibility of replacing or regenerating failing body parts with new tissues derived from stem cells has provoked hope, controversy and conflicting scientific claims.
- Embryonic stem cells offer primordial potential, but scientists are still struggling to understand and control them. Stem cells in the adult body may be easier to marshal for some tasks, but their true origin and range of abilities are still unresolved.
- Many hurdles, both scientific and political, remain before stem cell treatments can be widely applied to patients.

WHAT ARE EMBRYONIC STEM CELLS?

Embryonic stem (ES) cells are derived from the portion of a very early stage embryo that would eventually give rise to an entire body. Because ES cells originate in this primordial stage, they retain the "pluripotent" ability to form any cell type in the body.

CELL FATE

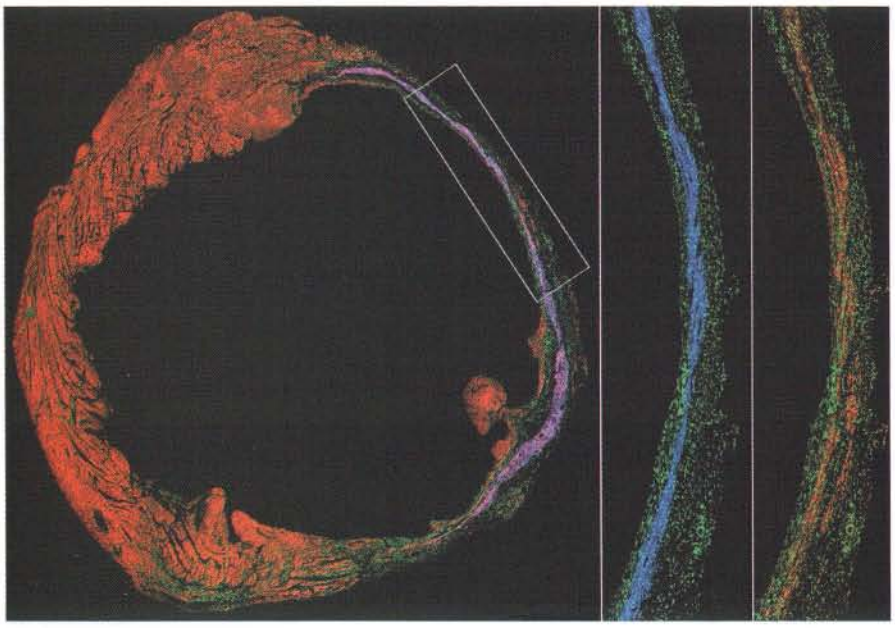
Less than a week after a human egg is fertilized, the developing embryo contains about 100 to 150 cells that have yet to differentiate. The embryo is a hollow ball, called a blastocyst, consisting only of an outer cell mass, which in a pregnancy would later form the placenta, and an inner cell mass (ICM), which would become the fetus. Inside a womb, these cells would continue multiplying, beginning to specialize by the third week. The embryo, called a gastrula at this stage, would contain three distinctive germ layers whose descendants would ultimately form hundreds of different tissue types in the human body.



MAKING EMBRYONIC STEM CELLS

To create ES cell lines, scientists remove the inner cell mass from a blastocyst created in the laboratory, usually left over from an attempt at in vitro fertilization. The ICM is placed on a plate containing feeder cells, to which it soon attaches. In a few days, new cells grow out of the ICM and form colonies (*above*). These cells are formally called embryonic stem cells only if they meet two criteria: they display markers known to characterize ES cells, and they undergo several generations of cell division, or passages, demonstrating that they constitute a stable, or immortalized, cell line.

ANDREW SWIFT



MOUSE HEART in cross section shows the left ventricle, where 38 percent of tissue destroyed by myocardial infarction (*first frame, rectangle*) was repaired by cloned stem cells within a month. Close-ups of the damaged area display cloned cells (*blue*) and new heart cells (*red*).

antigenic properties of the cells themselves can be reduced. But those feats have yet to be conclusively demonstrated. At present, the only sure way to circumvent the problem of immune rejection would be to create an ES cell line using a patient's own genetic material through nuclear transfer or cloning. This technique has inspired considerable controversy and has its own practical hurdles to overcome, but it has also produced encouraging results in animal experiments for regenerating failing tissues.

Turning Back the Clock

CLONING CAN BE VIEWED as a way to restore embryonic potential to a patient's old cells. The human body is made of more than 200 kinds of cells, and in mammals, once a cell is committed to a particular type, there is normally no turning back. It is said to be "terminally differentiated." An exception to this rule is when the nucleus containing an unfertilized egg's genetic material is extracted and the nucleus of a somatic (body) cell is placed into the egg instead. The egg is tricked into behaving as though it has been fertilized and begins dividing like a normal embryo. The ES cells derived from this embryo will contain the donor somatic cell's DNA. But the somatic cell will have been reprogrammed—reset to a state of stemness, capable of generating any tissue type.

One of us (Lanza) recently showed that partially differentiated stem cells from a cloned mouse embryo could be injected into the donor mouse's heart, where they homed in on the site of injury from a heart attack, replacing 38 percent of the scar with healthy heart tissue within a month [*see illustration above*]. And this year, for the first time, somatic cell nuclear transfer (SCNT) yielded a human ES cell line. A few in the scientific community had started to wonder whether the nuclear-transfer technique would work with primate physiology to produce therapeutic stem cells. But Woo Suk Hwang of Seoul National University and his colleagues proved that it could be done. The Korean team announced this past February that they had created a human embryo through SCNT, grew it into a blastocyst and derived a pluripotent ES cell line. Their accomplishment represents a major milestone. It also demonstrates how many unknowns we still face.

Because Hwang's group had 242 donated eggs to work with, they were able to experiment with techniques, timing and conditions at every step. Even so, from hundreds of eggs the effort yielded only a single ES cell line, and the researchers have said that they are not certain which of their methods was responsible for that success. Much remains to be learned about the mysterious mechanism of reprogramming within the egg and all that could go wrong while creating and culturing a nuclear-transfer embryo.

Scientists are still not sure whether reprogramming itself or other aspects of handling these embryos might introduce gene mutations that could predispose the resulting ES cells to senescence or cancer, and more research is needed to detect these potential problems. Inherited gene mutations, such as those that cause hemophilia or muscular dystrophy, would have to be corrected as well before using a patient's own cells to create ES cells. But techniques for gene-specific modifications routinely performed in mouse ES cells have been successfully applied to human ES cells, providing a means of safely correcting mutations before administering cells to patients.

The overall health of ES cells derived from clone embryos has also been questioned because efforts to produce live animals through cloning have met with an unusually high rate of deformities and mortality. When a cloned ES cell line's potential is tested by injecting the cells into a developing animal blastocyst, though, the resulting animals seem to be

THE AUTHORS

ROBERT LANZA and *NADIA ROSENTHAL* are leading stem cell researchers. Lanza is medical director of Advanced Cell Technology, Inc., as well as adjunct professor at the Institute of Regenerative Medicine at Wake Forest University School of Medicine. Lanza's current research centers on embryonic stem cells; he has also done groundbreaking work in cloning and tissue engineering. Rosenthal is head of the European Molecular Biology Laboratory in Rome. She directs the EMBL Mouse Biology program, concentrating her research on stem cell–mediated regeneration of neuromuscular and cardiac tissues, embryonic heart development, and developing mouse models of human diseases. Before joining EMBL, Rosenthal directed a laboratory at the Harvard Medical School's Cardiovascular Research Center and was a consultant on molecular medicine for the *New England Journal of Medicine*.

POLITICS: THE BIGGEST OBSTACLE OF ALL

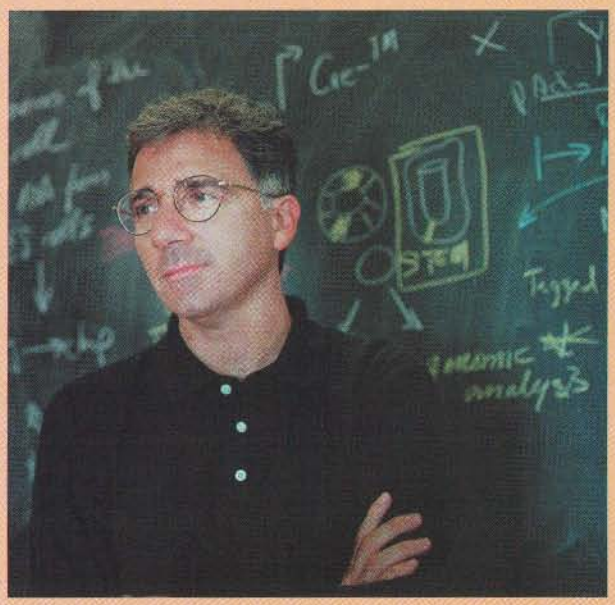
Research involving stem cells from the adult body is uncontroversial and unrestricted. But the versatility of adult stem cells is also the least proved. Many scientists believe that embryonic stem (ES) cells will provide more powerful treatments but that the greatest obstacle to assessing and harnessing the potential of ES cells is a lack of freedom and funding to do the work.

In the U.K., Singapore, South Korea, China, Japan and a handful of other nations, research on ES cells enjoys generous government support. The European Parliament, however, has been struggling to agree on a policy, leaving member countries to decide their own rules for now. A United Nations effort to draft a global convention has been deadlocked for two years.

U.S. scientists have been laboring under a partial ban decreed three years ago by President George W. Bush. Any researcher receiving government funding—the vast majority in both academia and industry do receive some kind of government grant money—may work only with embryonic stem cell lines created before the policy was announced in August 2001. The grantees can get federal support, but less than $20 million of the National Institutes of Health's $27-billion budget for 2003 actually went to fund studies using those so-called presidential cell lines.

The situation might as well be a total ban, according to many scientists. At present, only about 15 of the presidential lines are even available to researchers. Some of those are sickly and difficult to cultivate; others have started displaying genetic abnormalities. And all have spent time on a culture medium containing mouse cells, creating a possibility of contamination by nonhuman viruses. The U.S. Food and Drug Administration is now considering whether to allow clinical trials with these cells.

Since 2001, techniques for keeping ES cells alive have improved considerably, and scientists and their supporters in Congress have been clamoring for permission to produce new healthy lines. Some have not waited. Douglas A. Melton of Harvard University, whose two children have type 1 diabetes, is an outspoken critic of the current policy, and in February he announced that he had created 17 brand-new ES cell lines with private funds. He is making the lines freely available to researchers, but most investigators in the U.S. cannot afford to follow government regulations as Melton did by setting up a separate lab for his ES cell work, without so much as a federally funded pipette in it.



DOUGLAS A. MELTON of Harvard University created 17 ES cell lines from donated IVF embryos in a basement laboratory separate from his government-funded research. He will co-direct a new stem cell institute for which Harvard is seeking to raise $100 million.

A trend toward private funding of ES cell research may make it possible for more U.S. scientists to participate. Andrew S. Grove, founder of Intel, gave $5 million to the University of California at San Francisco to make new ES cell lines. Stanford University started an institute to study cancer using ES cells with a $12-million anonymous grant. The Howard Hughes Medical Institute and the Juvenile Diabetes Foundation funded Melton, and the Michael J. Fox Foundation for Parkinson's Research has given more than $5 million to institutions and individual researchers. But the political climate has driven many scientists away from the field entirely and has dampened investor enthusiasm, leaving some biotechnology firms struggling, too.

A few states are trying to turn the tide. Recognizing the potential windfall if ES cell research pays off, California was the first state to endorse stem cell studies officially, in 2002, and will hold a referendum in November seeking $3 billion in state funding for scientists. New Jersey added its endorsement last year and has promised $50 million over five years for the state's researchers.

—Christine Soares

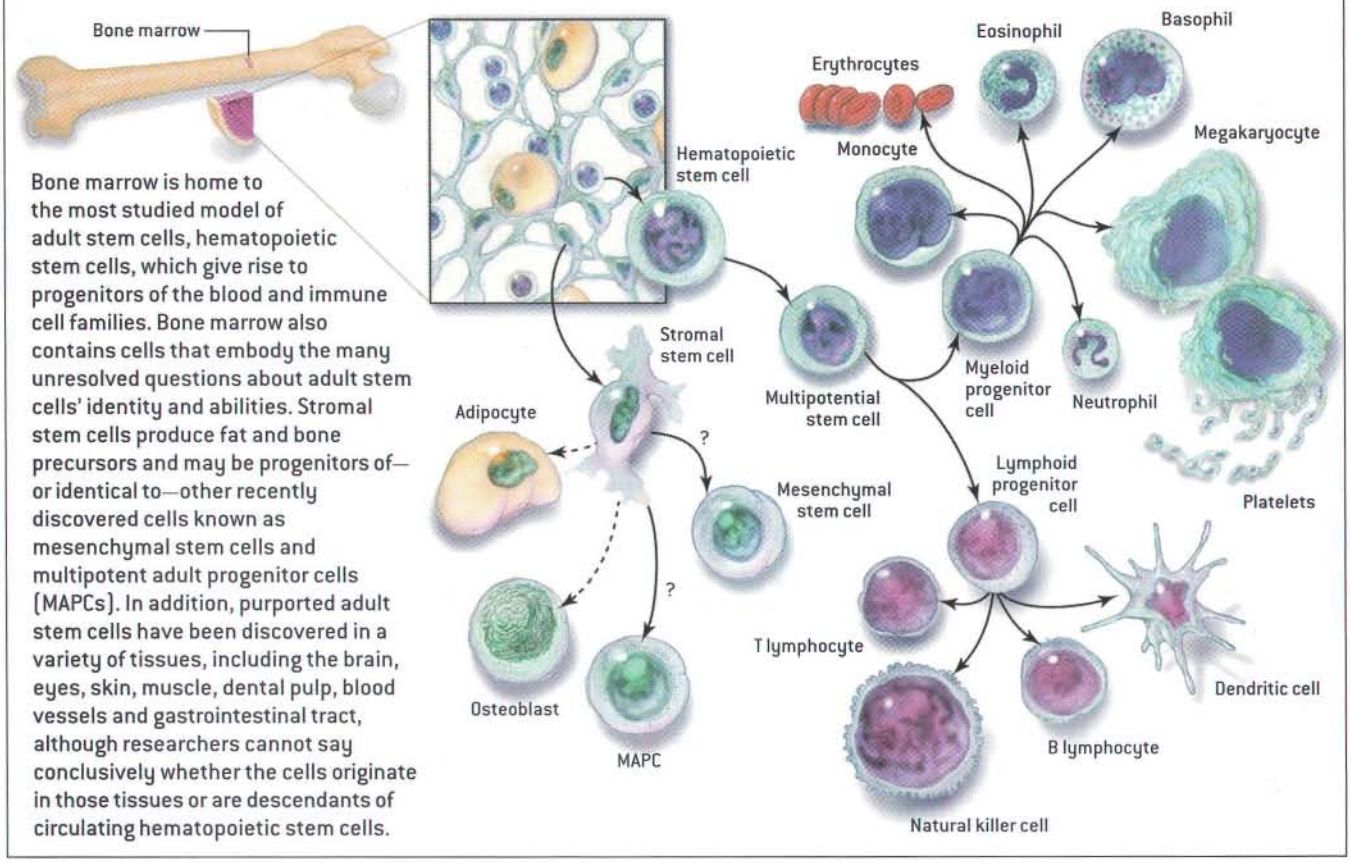
perfectly normal. This outcome suggests that although reproductive cloning is clearly too unpredictable to consider for humans, ES cells derived by nuclear transfer, at least for therapeutic purposes, are equivalent to regular ES cells.

Similar safety questions must also be resolved for a different technique that produces ES cells without nuclear-transfer or IVF embryos. In a process called parthenogenesis (from Greek for "virgin birth"), an unfertilized egg can be chemically tricked into beginning cell division as though it has been fertilized. These pseudo-embryos, or parthenotes, are considerably easier to grow than nuclear-transfer embryos. In animal studies, parthenotes have yielded ES cells able to differentiate into multiple tissue types in culture and to pass the teratoma test, forming cells from all three embryonic germ layers.

Unlike normal body cells, which contain a set of chromosomes from each parent, parthenotes contain a doubled set of the egg donor's chromosomes. This duplication gives a parthenote a full complement of genes but prevents it from being viable if it were implanted in a woman's womb. Having a single "parent" also means that parthenote cells carry half the normal potential combinations of antigens, making them much easier to match to patients. A bank of fewer than

KATHLEEN DOOHER/HOWARD HUGHES MEDICAL INSTITUTE

STEM CELL STOREHOUSE



1,000 parthenogenic ES cell lines could probably provide immunological matches for most of the U.S. population.

How long it will take for any ES cell therapies to be tested in humans will be determined as much by politics as by the remaining scientific questions [*see box on preceding page*]. Well-understood and easy-to-control cell types derived from ES cells, such as dopamine-producing neurons or the eyes' retinal pigment epithelium cells, could be ready for human trials in less than two years. In the meantime, the extraordinary regenerative potential of embryonic stem cells has intensified the search for similar cells that may be involved in normal healing in the adult body.

Hidden Potential?

SKIN BEGINS REPAIRING itself immediately after being injured. The human liver can regenerate up to 50 percent of its mass within weeks, just as a salamander regrows a severed tail. Our red blood cells are replaced at a rate of 350 million per minute. We know that prolific stem cells must be at work in such rapidly regenerating tissues. But their very vigor raises questions about why other organs, such as the brain and heart, seem incapable of significant self-repair, especially when purported stem cells have also recently been discovered in those tissues.

The best-known stem cells in the adult body are the hematopoietic stem cells found in bone marrow, which are the source of more than half a dozen kinds of blood cells. Their ability to generate a variety of cell types, at least within a specific tissue family, is why hematopoietic stem cells have been described as multipotent.

There is great hope that similar multipotent stem cells found in other body tissues might be drafted into repairing damage without the need to involve embryos—or better still, that an adult stem cell with more versatility, approaching the pluripotency of embryonic cells, might be discovered.

But scientists are just beginning to investigate whether natural regeneration is somehow blocked in tissues that do not repair themselves easily and, if so, whether unblocking their regenerative capacity will be possible. The very source, as well as the potential of various adult stem cells, is still disputed among researchers. We cannot say for sure whether tissue-specific adult stem cells originate within those tissues or are descendants of circulating hematopoietic stem cells. Nor do we know how far these cells can be pushed to differentiate into functional tissues outside their specific type or whether such transdifferentiation produced in the laboratory could be reproduced in a living organism.

The idea that certain adult stem cells might have greater potential first came from observations following human bone marrow transplants, when donor cells were subsequently found in a wide range of recipients' tissues. These accounts implied that under the right conditions, stem cells from the bone marrow could contribute to virtually any part of the body. (Similar claims have been made for the so-called fetal stem cells found in umbilical

ANDREW SWIFT

cord blood, which resemble hematopoietic stem cells.)

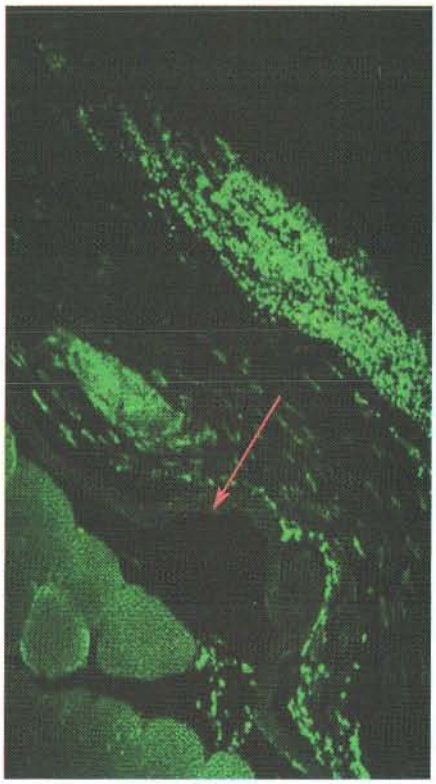
Attempts to directly test this theory in living organisms, however, have not found consistent evidence of such plasticity. In March separate reports from Leora Balsam and her colleagues at Stanford University and from a group led by Charles E. Murry of the University of Washington both described using powerful tracking methods to see if hematopoietic stem cells would incorporate into injured heart muscle, a nonhematopoietic tissue. Neither group detected contribution of new tissue by the stem cells.

What has increasingly been found is extensive fusion of bone marrow stem cells to cells in the heart, liver and brain, offering an alternative explanation for the presumed transdifferentiation. In future studies of adult stem cell potential, it will be crucial to rule out the possibility that stem cells are merely fusing to local cells rather than generating new ones.

Still, tissue-specific cells have already produced encouraging results. In the German TOPCARE-AMI study of patients with severe heart damage following myocardial infarction, the patients' own heart progenitor cells were infused directly into the infarcted artery. Four months later the size of the damaged tissue swath had decreased by nearly 36 percent, and the patients' heart function had increased by 10 percent.

The small number of stem cells that can be isolated from any adult tissue remains the biggest technical hurdle to applying this type of research more widely in the clinic. In mouse bone marrow, stem cells are as rare as one in 10,000, and the ratio may be even greater in humans. In most tissues, there is no predictable location for stem cells, and we possess only limited tools for identifying them using surface markers or gene expression signatures.

Once isolated, adult stem cells are also notoriously slow and labor-intensive to grow. As is true of embryonic cells, so little is understood about the factors that may control the adult stem cells' fate that we do not yet know whether extensive time spent in culture could harm their ability to restore tissues in patients.



ANTONIO MUSARÒ ET AL. IN *PNAS*, VOL. 101, NO. 5, PAGES 1206–1210; FEBRUARY 3, 2004. ©2004 NATIONAL ACADEMY OF SCIENCES, U.S.A.

BONE MARROW STEM CELLS marked with green fluorescence migrated to leg muscle that was producing the injury-alarm protein IGF-1 (insulinlike growth factor). The stem cells homed toward the damaged area (*arrow*), where they initiated tissue regeneration.

Rather than hunting for a patient's stem cells to remove, cultivate and then replace them, we may be able to summon the body's hidden stores. Increasing evidence suggests that stem cells, like metastatic tumor cells, respond to common chemical signals leading them to sites of injury. One of us (Rosenthal) recently showed in mice that stem cells will travel great distances to reach an injury when summoned with the help of a protein called IGF-1 [*see illustration above*].

Marshaling the body's own ability to trigger tissue regeneration by stem cells will require a better grasp of the roles played by such chemical signals. Rosenthal and her collaborator Antonio Musarò have demonstrated that IGF-1 helps to beckon stem cells, but we suspect that this molecule may also take part in causing some of the injured cells to revert to a multipotent state and begin differentiating into the required tissue types. This phenomenon, known as epimorphic regeneration, underlies the ability of newts and zebra fish to regrow entire limbs and organs.

Regenerative medicine's ideal would be to find a means to cause such controlled dedifferentiation of adult tissue—in essence turning a terminally differentiated cell back into a stem cell. Many researchers are looking for the magic molecules that can produce this transformation, and some very preliminary successes have recently been reported. But therapeutic regeneration through dedifferentiation is a long way off and will most likely come from a much better understanding of stem cells themselves—both adult and embryonic.

Which Way Forward?

AS OFTEN HAPPENS in science, stem cell research has raised as many new questions as it has answered, but the field is advancing. Early tests of human adult stem cells in treating cardiovascular disease are encouraging and will certainly lead to more extensive trials in the near future. Given much promising experimental evidence in animals, therapeutic trials of human ES cell derivatives in neurodegenerative disease are probably imminent.

As the appropriate source of cells for both research and eventual therapeutic applications continues to be hotly debated, restrictions on this research are slowing progress. But we believe that generating replacement cells and regenerating organs are feasible and realistic goals. The remaining hurdles are difficult but not insurmountable. SA

MORE TO EXPLORE

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Nuclear Explosions in Orbit

The spread of nuclear weapons and ballistic missiles raises fears of atomic attacks on the global satellite system

By Daniel G. Dupont

On July 9, 1962, U.S. military researchers on a tiny Pacific atoll called Johnston Island fired a thermonuclear weapon into outer space. Code-named Starfish Prime, the launch onboard a Thor ballistic missile was the latest of a series of similar classified tests the U.S. Defense Department had begun four years before. But as the rocket rose on its smoky plume, few on the launch team realized that the forthcoming 1.4-megaton orbital burst was to yield surprising long-term results.

Hotel operators in Hawaii, some 1,300 kilometers away, were expecting a good show, though. Word had leaked of this latest "rainbow bomb" test shot, so a few enterprising resorts had organized rooftop parties from which guests could better view the distant fireworks. When the warhead detonated that evening at an altitude of 400 kilometers, it produced a brilliant white flash that momentarily lit up sea and sky like a noonday sun. Then, for about a second, the heavens turned light green.

Other Hawaiians witnessed some less welcome aftereffects. Streetlights suddenly blinked out on the island of Oahu. Local radio stations shut down, and telephone service failed for a time. Elsewhere in the Pacific, very high frequency communications systems malfunctioned for half a minute. Scientists later realized that Starfish Prime had sent a strong, disruptive electromagnetic pulse (EMP) sweeping through the vast region below the blast.

During the next several minutes, a blood-red aurora spread across the horizon [*see illustration on opposite page*]. Scientists had anticipated this stage of the process; each previous orbital test had left an artificial cloud of charged particles in space. Eventually the planet's magnetic forces molded the energetic clouds into globe-girdling belts that resembled its natural Van Allen radiation belts [*see illustration on page 71*]. But almost no one expected what happened during the following months: the intense man-made belts crippled seven low earth orbit (LEO) satellites, a third of the

DEFENSE THREAT REDUCTION AGENCY

ARTIFICIAL AURORA appeared a few minutes after a 1.4-megaton hydrogen bomb exploded 400 kilometers above the Pacific Ocean during a 1962 U.S. test called Starfish Prime. Excited atomic oxygen produced the striking red glow.

planet's fleet at the time. U.S. military researchers went on to conduct three more high-altitude nuclear explosions (HANEs) later that year but then stopped when the Cuban Missile Crisis led to the signing of the Atmospheric Test Ban Treaty.

HANE Alert

SINCE THE EARLY HANE TESTS, relatively little has been said in public about the threat such events pose to the growing constellation of satellites that today provides critical communications, navigation, broadcast and cable television, and earth-imaging and weather-forecasting services. Some 250 commercial and military satellites now orbit in the lowest altitudes, according to the Satellite Industry Association, and most of them are defenseless against the radiation that would be released by a high-altitude atomic burst. As knowledge of nuclear-weapon and ballistic-missile technology proliferates among potential adversary states and, perhaps, terrorist groups, concerns mount for the future of the global satellite system. One small atomic warhead detonated at the optimum altitude over the U.S. "could have a very serious effect on communications, electronics and all sorts of systems—a devastating effect on our society and everyone else's, too," states Robert S. Norris, senior research associate with the Natural Resources Defense Council's nuclear program.

The prerequisites for a nation, or a nonstate entity, to conduct a HANE are relatively straightforward: a small nuclear weapon and a standard ballistic-missile system, something not much more sophisticated than a SCUD. Eight countries—the U.S., Russia, China, the U.K., France, Israel, India, Pakistan and probably North Korea—now possess such a capability. It appears that Iran is also close to acquiring the necessary technology, some Pentagon analysts say.

In 2001 a space policy committee chaired by Donald H. Rumsfeld (before he became secretary of defense) warned that "the U.S. is an attractive candidate for a 'Space Pearl Harbor.'" Further, the group (formally the Commission to Assess United States National Security Space Management and Organization) called for the country's leaders to act soon to reduce America's exposure to a surprise attack in orbit and to limit the consequences of such an event.

U.S. MILITARY SCIENTISTS conducted the Teak test in 1958 to evaluate antiballistic-missile effects. The 3.8-megaton, 77-kilometer-high blast halted radio communications throughout the Pacific and even grounded civilian and military aircraft in distant Hawaii.

Even though the U.S. is installing a missile defense system designed to defend against long-range strikes, the system is unproved and may never be able to fully protect the nation. Ironically, use of an antimissile interceptor against a nuclear-tipped target with a proximity fuse could in fact set off a destructive HANE phenomenon.

The Pentagon's Defense Threat Reduction Agency (DTRA) attempted to predict the results of various hypothetical scenarios involving the use of HANEs against LEO satellites in 2001. The shocking conclusion: a single low-yield nuclear weapon (10 to 20 kilotons, the size of the Hiroshima bomb) detonated between 125 and 300 kilometers above the earth's surface "could disable—in weeks to months—all LEO satellites not specifically hardened [protected] to withstand radiation generated by that explosion." K. Dennis Papadopoulos, a plasma physicist at the University of Maryland who studies the effects of HANEs for the U.S. government, puts it slightly differently: "A 10-kiloton nuclear device set off at the right height would lead to the loss of 90 percent of all low-earth-orbit satellites within a month."

A high-altitude atomic explosion could raise peak radiation levels in parts of low earth orbit by three to four orders of magnitude, the DTRA report found. Models cited by the Defense Department study group indicate that radiation flux levels could remain elevated for two years. Any satellites in the affected region would accumulate radiation exposure much more quickly than they were designed to do, slowing electronic switching speeds and raising power requirements. The first subsystems to go, according to the study, would most likely be a satellite's attitude-control electronics or its communications links. "Eventually," it states, "the active electronics fail and the system becomes incapable of performing its mission." Although some un-

Overview/*Orbital Nukes*

- The launch and detonation of a nuclear-tipped missile in low earth orbit could disrupt the critical system of commercial and civil satellites for years, potentially paralyzing the global high-tech economy.
- More nations (and maybe nonstate entities) will gain this capability as nuclear-weapon and ballistic-missile technology spreads around the world. The possibility of an attack is relatively remote, but the consequences are too severe to be ignored.
- In the event of a nuclear explosion in space, clever manipulation of very low and extremely low frequency electromagnetic waves may reduce the number of charged particles resulting from the blast, clearing the way for renewed satellite operations.

DEFENSE THREAT REDUCTION AGENCY

shielded satellites would survive, their useful life spans would be shortened dramatically.

Meanwhile the high radiation levels would preclude the launch of replacement spacecraft. The study notes that "the manned space program would have to stand down for a year or more as radiation levels subside." It also concludes that the side effects of a HANE could lead to more than $100 billion in replacement costs—and this estimate does not even begin to account for the damage to the global economy from the loss of so many crucial space assets. Despite the recent scrutiny, however, the threat of HANEs has not been given "anywhere near the attention it deserves," cautions Representative Curt Weldon of Pennsylvania, a longtime advocate for missile and nuclear defense on the House Armed Services Committee.

Low Earth, High Risk

THE AMERICAN AND SOVIET HANE TESTS of the 1950s and 1960s remain the only real-world examples of the phenomenon for today's scientists to examine. Researchers know that a nuclear fireball is a rapidly expanding sphere of hot gases that sends forth a supersonic shock or blast wave. At the same time, the fireball radiates tremendous amounts of energy in all directions in the form of thermal radiation, high-energy x-rays and gamma rays, fast neutrons, and the ionized remnants of the fission device itself. Near the ground, the atmosphere absorbs the emitted radiation, a process that heats the air to the exceptionally high temperatures required to set a fireball alight. The air molecules also attenuate to some degree the generation of an electromagnetic pulse. Any immediate destruction wreaked by a near-earth burst comes from pulverizing shock waves, violent winds and hellish heat.

High-altitude nuclear blasts produce significantly different effects. In the lower reaches of vacuous space, the resulting fireball grows much larger and faster than it does near the ground, and the radiation it emits travels much farther.

The strong EMP that results has several components, according to Papadopoulos. In the first few tens of nanoseconds, about a tenth of a percent of the weapon yield appears as powerful gamma rays with energies of one to three mega-electron volts (MeV, a unit of electromagnetic energy). The gamma rays rain down into the atmosphere and collide with air molecules, depositing their energy to produce huge quantities of positive ions and recoil electrons (also known as Compton electrons). The impacts create MeV-energy Compton electrons that then accelerate and spiral along the earth's magnetic field lines. The resulting transient electric fields and currents that arise generate electromagnetic emissions in the radio-frequency range of 15 to 250 megahertz (MHz, or one million cycles per second). This high-altitude EMP occurs between 30 and 50 kilometers above the earth's surface.

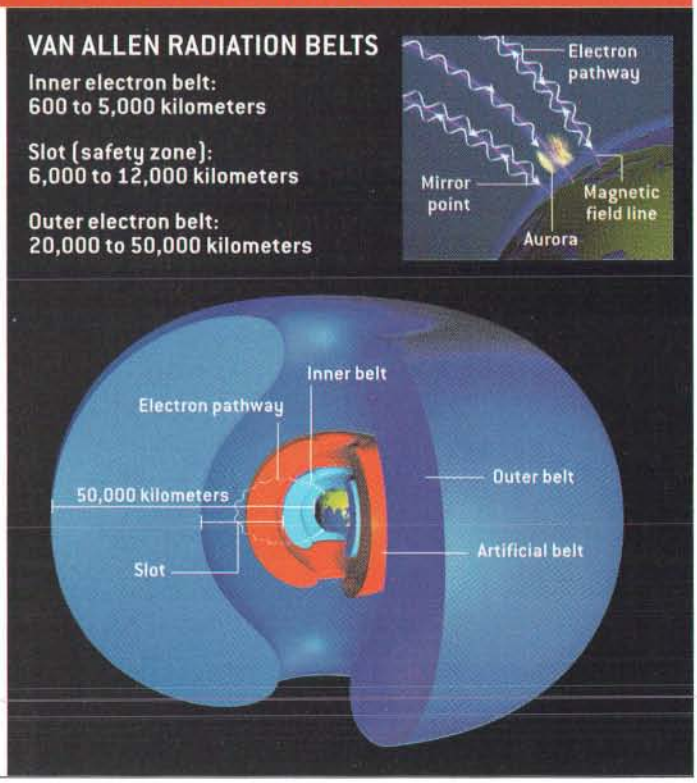
The size of the emitting region depends on the altitude and yield of the nuclear burst. For a one-megaton explosion at 200 kilometers in altitude, the diameter is about 600 kilometers, Papadopoulos states. The high-altitude EMP can create electric potentials that can exceed 1,000 volts—enough to cripple any sensitive electrical infrastructure on the ground that is within

EARTH'S MAGNETIC NEIGHBORHOOD

Our planet's dipole magnetic field steers electrons captured from the solar wind (or injected by nuclear detonations) from one pole to the other and back along helical paths that follow field lines like beads on a wire. The magnetic field thus constrains electrons into toroidal (doughnut-shaped) Van Allen belts that girdle the globe.

Between the inner and outer natural belts is the "slot"—a zone relatively free of charged particles in which satellites can safely orbit. When nuclear explosions "pump" the belts with an overflow of electrons, artificial belts can form in the slot that can disrupt satellite electronics.

When an electron approaches the terminus of a magnetic field line, near the poles where magnetic forces are stronger, it slows down (*detail*). Eventually the particle halts and reflects back out into space along the field line from what is called the particle's mirror point. The altitude of a mirror point depends on a particle's pitch angle—the angle between its linear motion along the field line and its spiral motion around the line—at the equatorial plane. Particles with pitch angles more parallel to the magnetic field lines than perpendicular reach mirror points below 100 kilometers, where they can collide with atmospheric gas molecules and fall to the ground, often yielding an aurora (*center pathway*). If the mirror point is 100 kilometers or higher, the particle is unlikely to strike the air and will remain trapped in the planetary magnetic field.



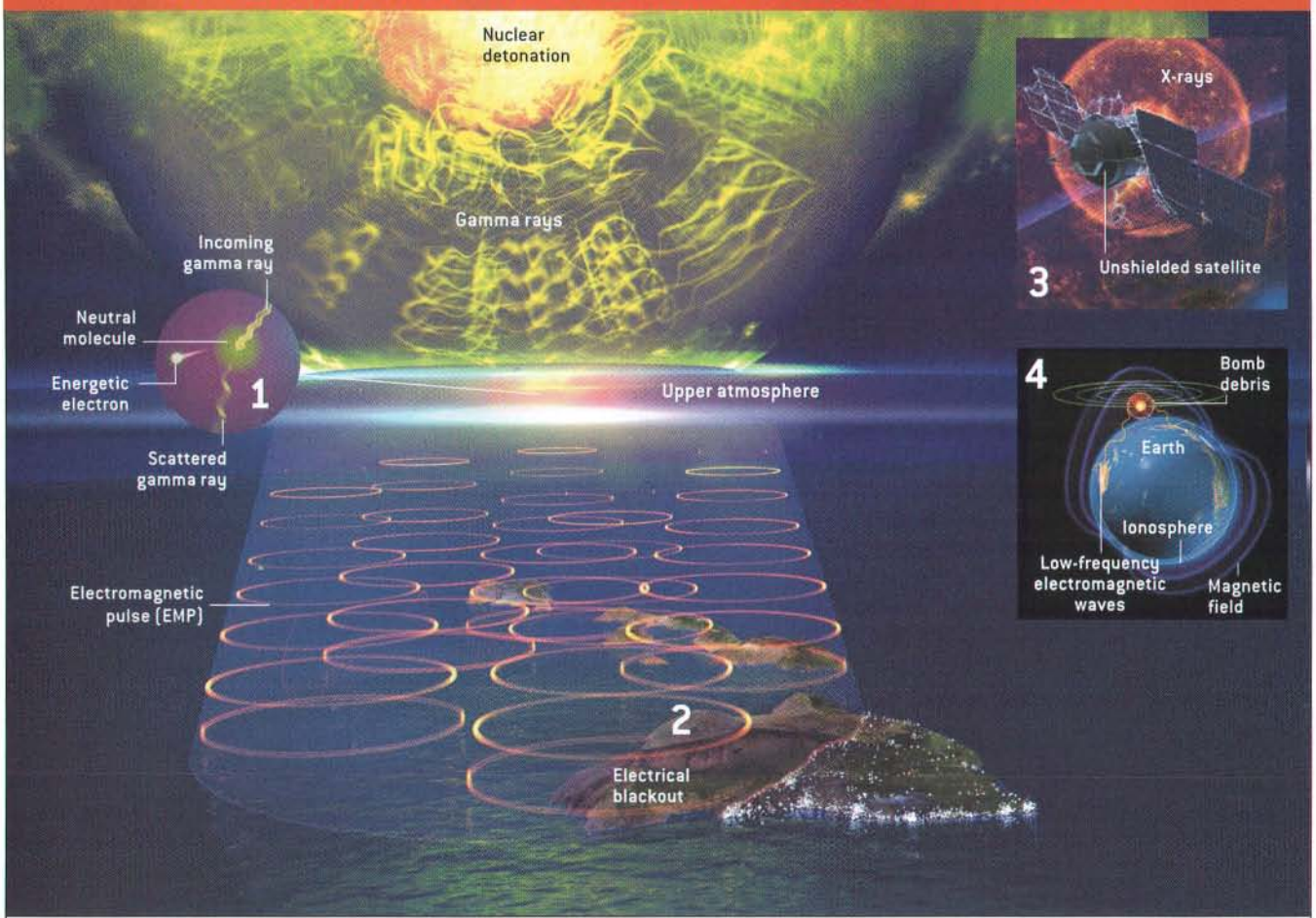
direct line of sight. At orbital elevations, EMP fields are small and generally cause little interference, he adds.

In unclassified documents, U.S. government scientists estimate that at least 70 percent of a fission bomb's yield typically emerges as x-rays. These x-rays, as well as the accompanying gamma rays and high-energy neutrons, strike everything within line of sight, doing severe damage to nearby satellites. The radiation's energies decrease with distance, diminishing the effect on satellites farther away from the fireball.

"Soft," or low-energy, x-rays produced by a HANE would not penetrate deeply into any spacecraft they encountered. Instead they would generate extreme heat at the outer surfaces, which itself could harm the sophisticated electronics inside. Soft x-rays would also degrade solar cells, impairing a satellite's ability to generate power, as well as damaging sensor or telescope apertures. When high-energy x-rays strike a satellite or other system components, however, they create strong internal electron fluxes that produce strong currents and high voltages that can fry sensitive electronic circuitry.

Soon after this point, ionized bomb debris from the blast interacts with the earth's magnetic field, pushing the field out to a radius of 100 to 200 kilometers, Papadopoulos explains.

AFTERMATH OF AN ORBITAL NUCLEAR EXPLOSION



After an atomic weapon detonates in orbit, the following sequence of events typically occurs. In the first few tens of nanoseconds, powerful gamma rays emerge and strike neutral molecules 30 to 40 kilometers up in the upper atmosphere (*1*). The collisions yield high-energy electrons. These fast-moving charges generate a strong electromagnetic pulse that can disable any sensitive electronics within direct line of sight on the ground (*2*).

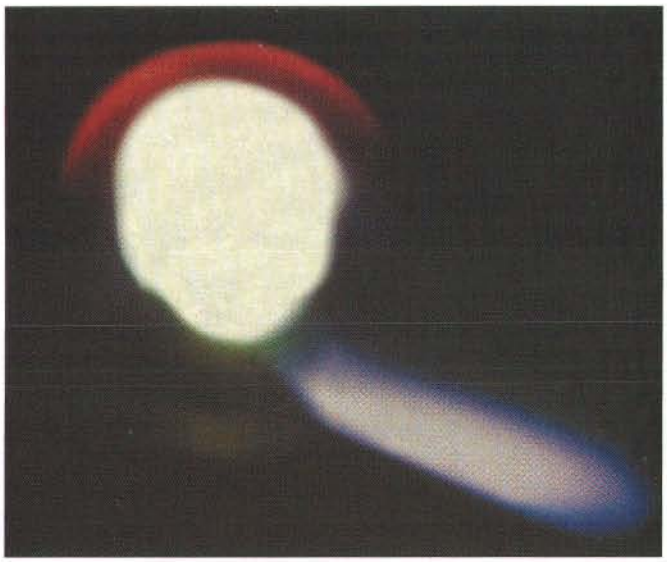
During the next second after the burst, most of the nuclear warhead's energy sprays out as energetic x-rays (*3*). When these powerful electromagnetic waves strike unshielded satellites nearby, they induce large currents and voltages that, in effect, cook the sophisticated electronic devices inside.

At the same time, bomb debris that has been ionized by the expanding fireball is driven upward a few hundred kilometers. These charged particles interact with the earth's magnetic field to produce low-frequency electric field emissions (*4*). The field's slowly oscillating waves reflect back and forth off the earth's surface and the underside of the ionosphere and thus propagate around the planet. Although this electric field is weak, it can nonetheless induce high voltages in long terrestrial and underwater cables, disrupting electric circuits far from the blast.

During the next few weeks and months, energetic electrons trapped in orbit degrade the operations of electrical systems in the additional satellites they eventually encounter (*not shown*).

This moving electromagnetic field gives rise to a low-frequency electric field pulse. These slowly oscillating waves reflect back and forth off the earth's surface and the underside of the ionosphere, propagating around the globe. Although the magnitude of the electric field is small (less than a millivolt per meter), it can generate large voltages in long terrestrial and underwater cables, triggering widespread disruption of electric power circuits. This phenomenon caused the failures in the electrical and telephone systems on the Hawaiian Islands after the Starfish Prime test.

After the immediate effects, the extensive cloud of energetic electrons and protons released by a HANE is accelerated by the earth's magnetic field into the magnetosphere, pumping up the sizes of the naturally occurring Van Allen radiation belts that surround the planet. These charged particles also leak into the area between the natural belts, forming artificial radiation belts—an effect named for Nicholas Christofilos, the scientist who forecast it in the mid-1950s. A series of high-altitude detonations designated the Project Argus tests, conducted by the U.S. in the late 1950s, confirmed his hypothesis. Christofilos saw potential military utility in man-made radiation belts, which he thought might be able to block radio communications or even disable incoming ballistic missiles.



IN THE KINGFISH TEST, a U.S. Thor missile carried a nuclear warhead (with a yield less than 1,000 kilotons) to a height of 97 kilometers. Shock-excited oxygen atoms produced the red glow. The phenomenon at the bottom resulted from high-energy beta particles striking the relatively dense air at lower altitudes. This 1962 shot disrupted radio communications over the central Pacific for three hours.

Shielding Satellites

THE PENTAGON has been working for decades to safeguard its orbital assets against the effects of nuclear explosions. Many key military satellites have been placed in high orbits and are thus considered relatively safe against nuclear events. Moreover, engineers install protective shields to harden military satellites against radiation. These metallic enclosures attempt to defend the vulnerable electronics inside by forming Faraday cages—sealed conductive boxes that exclude external electromagnetic fields. Satellite builders surround sensitive components with metallic (often aluminum) shielding layers that can attenuate the flow of electrical charge. The aluminum sheets range in thickness from less than 0.1 to one centimeter. Ground-based weapons, communications and other critical systems are insulated against EMP effects as well.

Hardening satellites is a costly endeavor, however. Greater protection means more expense and more massive protective materials. And heavier satellites cost significantly more to launch. Just in the design phase, hardening efforts add 2 to 3 percent to the multimillion-dollar price tags of satellites, Defense Department sources affirm. According to some estimates, installing the shielding panels and hardened components and launching the extra weight can add from 20 to 50 percent to the total cost of a satellite. Finally, electronic components capable of withstanding the high radiation levels of a HANE—about 100 times as great as natural levels—offer functional bandwidths only about one tenth the size of those offered by commercially available processors, a fact that can raise operating costs by an order of magnitude.

Yet shields can do only so much, Papadopoulos reports. Designers say that the worst problem caused by a HANE's radiation is deep dielectric charging from the MeV-energy electrons. This destructive charge buildup can occur when high-energy particles penetrate spacecraft walls or protective shielding and then bury themselves in the dielectric semiconductor materials in microelectronics or solar cells. These interlopers lead to false system voltages and catastrophic discharges. If metal shielding exceeds a centimeter, electromagnetic protection declines drastically, he explains, because impacts by energetic particles can cause strong electromagnetic Bremsstrahlung radiation that can result in extensive damage. (*Bremsstrahlung* is German for the "braking radiation" produced when a charged particle decelerates rapidly as a result of collision with another body.)

Spacecraft can be protected in other ways, says Larry Longden of Maxwell Technologies, a company that shields satellites. Sensors can be installed to detect the presence of harmful radiation. A satellite equipped with such a device can be cued to shut down its computer processors and electronic circuits to wait for the destructive episode to pass. Despite the risks to civil orbiters, however, the Defense Department so far has failed to persuade U.S. satellite builders to harden their spacecraft voluntarily, states Barry Watts, senior fellow at the Center for Strategic and Budgetary Assessments.

THE AUTHOR

DANIEL G. DUPONT has covered national security and science and technology issues for more than 11 years. He is the editor of InsideDefense.com, an online news service, and publisher of the *Inside the Pentagon* family of newsletters. His articles have appeared in the *Washington Post, Mother Jones, Government Executive,* mediabistro.com and elsewhere, and he is a frequent contributor to *Scientific American.* A native New Englander, Dupont lives in Arlington, Va., with his wife, Mary, and their three sons.

Cleaning Up after HANEs

IF AN ADVERSARY succeeded in detonating a nuclear device in space today, the U.S. would be at a loss to remediate its long-term effects. Down the road, though, cleanup techniques now being studied might do the job. One approach is to eliminate harmful radiation "more quickly than nature would," says Greg Ginet, a program manager at the Air Force Research Laboratory. Researchers at the facility, along with others funded by the Defense Advanced Research Projects Agency (DARPA), are investigating whether generating very low frequency radio waves in space might send the resulting radiation out of orbit more rapidly.

To understand how that procedure might work, Papadopoulos says, it helps to consider an analogy. The earth's radiation belts in some ways resemble leaky buckets. Planetary magnetic forces pump energetic particles, or plasma, into the buckets. The rate at which they leak out depends on the amplitude of very low frequency (VLF, or between one hertz and 20 kilohertz) electromagnetic waves in the vicinity. A nuclear explosion, however, overfills the buckets, creating the artificial belts. The key to removing the plasma more rapidly from the magnetosphere is to increase the rate at which the radiation leaks out into the atmosphere, a process akin to widening the hole in the bottom of the buckets.

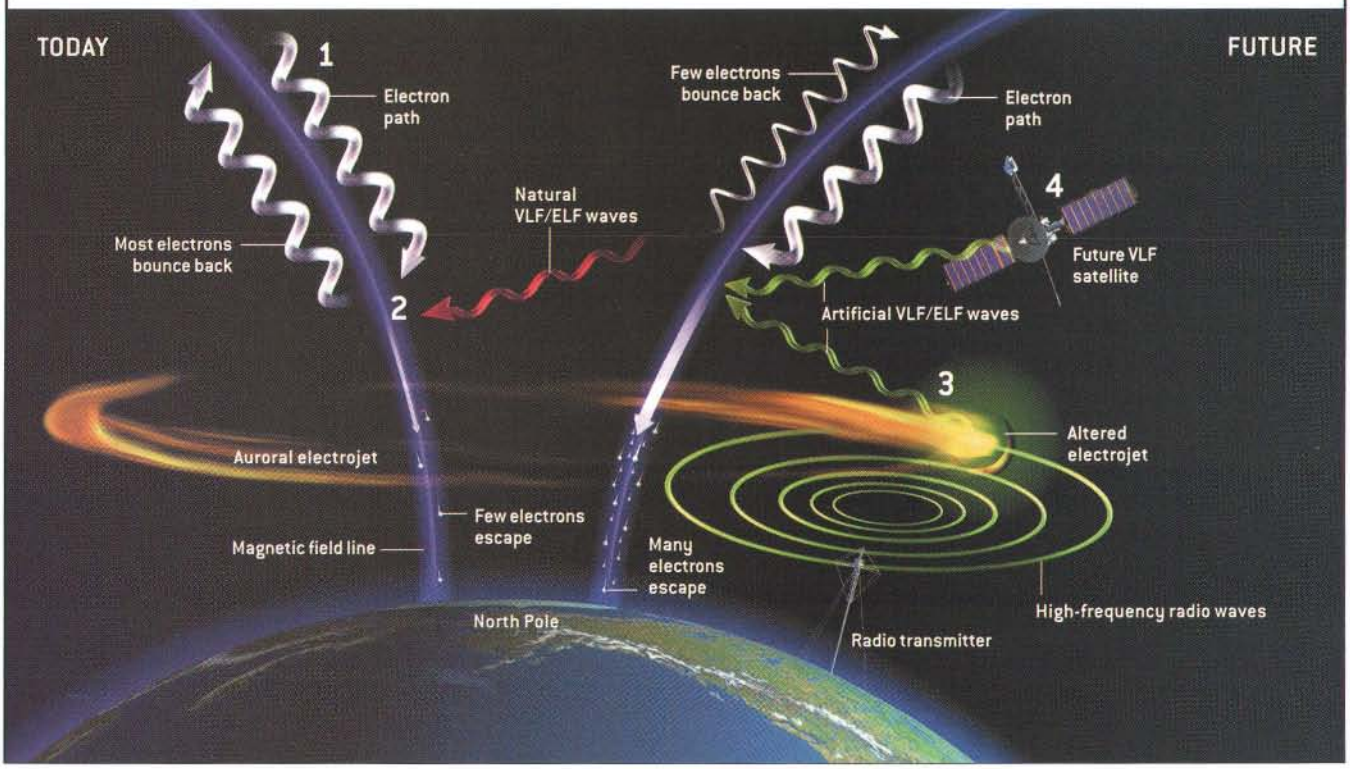
One way to do this, scientists say, would be to deploy a fleet of satellites designed to inject radiation belts artificially with VLF waves. To that end, DARPA and the U.S. Air Force are experimenting with the VLF transmitters at the High Frequency Active Auroral Research Project (HAARP) facility in Gakona, Alaska. HAARP is devoted to the study of the ionosphere—or, more specifically, how the ionosphere can be manipulated by man-made means. The facility it is being expanded in part to provide the Pentagon with a way to test whether it can reduce the population of charged particles in the earth's radiation belts.

HAARP researchers are trying to determine how many satellites might be needed for a global mitigation system. They are buoyed in this effort by work conducted by Stanford University during the 1970s and 1980s. Stanford scientists injected VLF

EASING THE EFFECTS OF AN ORBITAL BURST

A destructive radiation belt formed by an orbital nuclear explosion can take years to dissipate. Its life span depends on how rapidly the belt's electrons escape the earth's magnetic field. Most of these trapped electrons bounce back and forth between regions high above the planet's poles along magnetic field lines (*1*). When naturally occurring very low frequency (VLF) and extremely low frequency (ELF) waves strike some of these electrons in the vicinity of the poles, they deflect them, which increases the likelihood that they will drop to the earth's surface (*2*).

Researchers have learned that resonance-based interactions with these electrons can significantly amplify the VLF and ELF waves, which in turn boosts the rate of electron loss. By beaming high-frequency radio transmissions intermittently at the auroral electrojet—a natural electric current in the ionosphere 100 kilometers above the poles—they can alter its flow and thus generate VLF and ELF waves artificially (*3*). Mitigating the effects of an orbital burst could someday be accomplished by launching satellites that radiate VLF and ELF waves (*4*).



ALFRED T. KAMAJIAN

waves into the Van Allen belts using a transmitter located near the South Pole, and those waves, they found, were sometimes significantly amplified by the trapped electrons in the belts. This amplification occurs by tapping the free energy associated with the trapped particles, Papadopoulos notes. The resonance-based process is analogous to the electron-stimulation effect that occurs in free-electron lasers where a "wiggler" magnet accelerates electrons so that they emit synchrotron radiation.

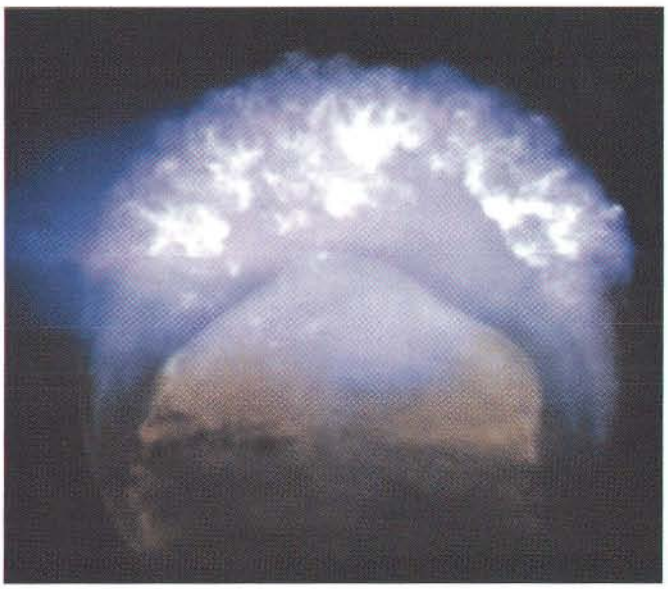
This amplification phenomenon lies at the heart of the HAARP effort. By boosting the VLF waves sent out by a fleet of satellites using natural means, the U.S. could employ far fewer emitting spacecraft, which could save billions of dollars. Defense Department researchers have shown that this amplifying effect could cut the number of satellites needed from more than 100 to fewer than 10.

Scientists have demonstrated that the facility can generate extremely low frequency (ELF) and VLF waves and inject them efficiently into the radiation belts [*see illustration on opposite page*]. It does this by periodically altering the flow of the auroral electrojet—a natural current that exists in the ionosphere some 100 kilometers overhead. The modulation, which produces a virtual ELF and VLF antenna in the sky, is accomplished by periodically turning on and off a high-frequency transmitter to change the temperature and thus the conductance of the plasma current. Researchers expect the completed facility to have sufficient power to determine whether the amplification and mitigation scheme can work. A space experiment to test these hypotheses may be conducted later this decade, according to Ginet, but any operational ground or satellite system is years beyond that.

How Remote a Threat?

A NUMBER OF GEOPOLITICAL scenarios could lead to a HANE incident. The DTRA study emphasized the hazards arising from a HANE as a warning shot to display a nation's resolve to fight and as a deterrent against attack. Using the lingo and modeling techniques of military planners, the DTRA group tackled two primary scenarios, both set in 2010. In one example, Indian armored forces cross the Pakistani border during a clash over the fate of Kashmir. The Pakistani government responds by detonating a 10-kiloton weapon 300 kilometers over New Delhi, high enough to avoid destructive ground effects but low enough to demonstrate clearly the ability to launch a deadly nuclear attack. Another case study has North Korea facing possible invasion, so its leaders order the explosion of a nuclear warhead above its own territory as a demonstration of the country's determination to resist. A U.S. missile defense system engages and destroys the booster rocket, but the warhead explodes 150 kilometers above the earth.

John Pike, who runs Globalsecurity.org, a defense watchdog organization, envisions a scenario in which North Korea decides to test its nascent nuclear arsenal—in space. "Most people assume that if North Korea conducts a test, it would be an underground test," he says. "That would not be my advice to [North Korean leader] Kim Jong Il."



ORANGE WAS THE CODE NAME for a 1958 burst of a 3.8-megaton nuclear device at an altitude of 43 kilometers. The test had little effect on radio communications and electrical systems in the Pacific area.

Experts have considered other possible plots, some of which involve detonations over the U.S. Very few countries are capable of this type of attack from their home soil, and such an attempt is unlikely. A mobile, sea-based platform, however, could be used to launch a crude missile with a small atomic payload that could still do significant damage. Although it is extremely difficult to assess the probability of these kinds of situations (remote though they may be), the consequences are so devastating that they cannot be ignored.

In addition to the enormous damage a HANE would cause, there is the question of response. A nuclear attack on the U.S. or an ally would provoke an immediate military reply, but what about a HANE? Weldon, who for years has been pondering that question—what he calls an "ethical dilemma"—has no answer. "From a moral standpoint, does the detonation of a nuclear warhead in space justify going in and killing people?" he asks. "Does that justify a nuclear response? Probably not." SA

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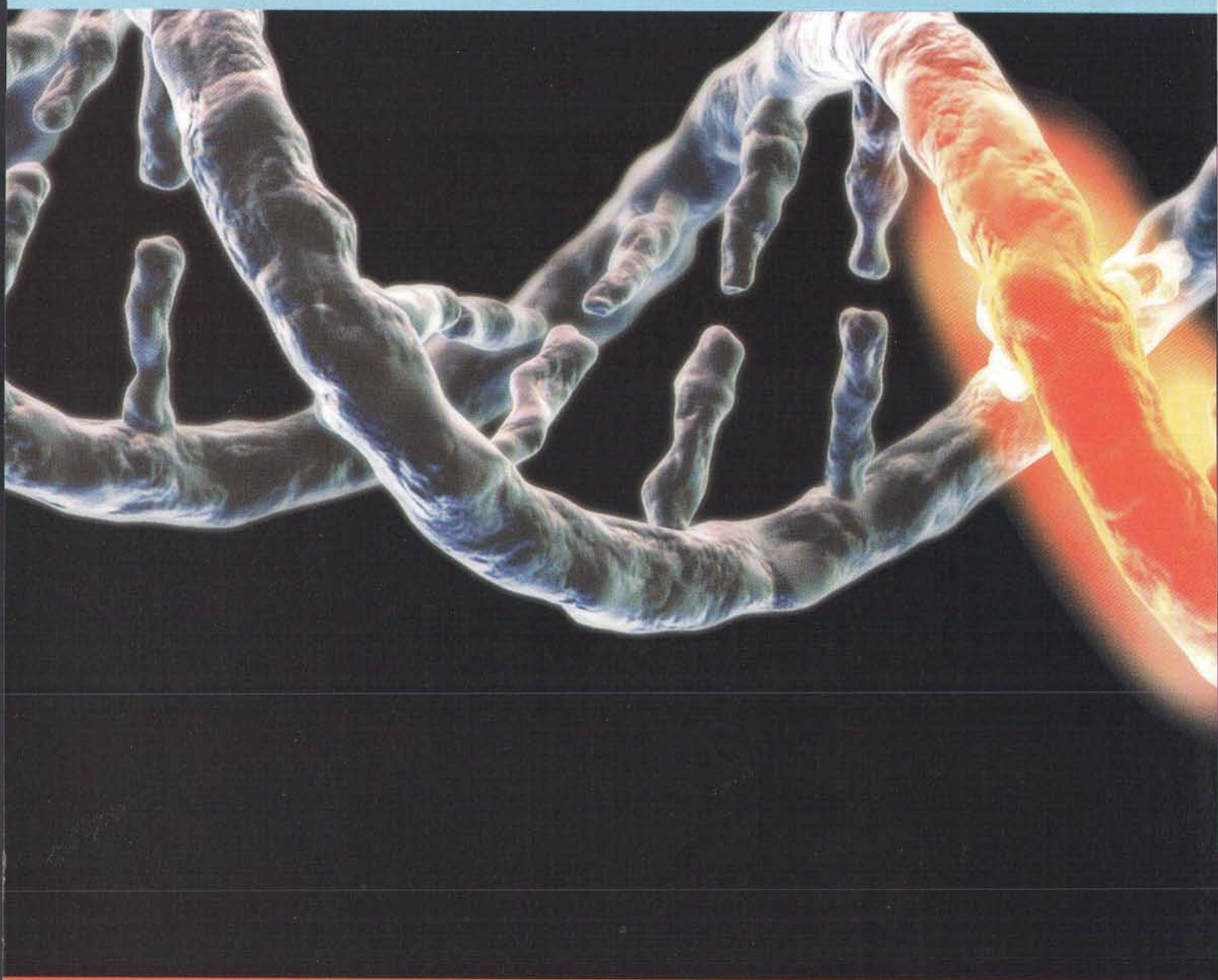

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SUBMARINE STEALTH

Deep Silence

The USS *Miami* nuclear submarine is 362 feet long, weighs 395 tons and is thrust by 35,000-horsepower engines. Yet the sound it radiates into the sea is little more than the hum of a kitchen refrigerator.

The ocean can be a noisy place: collapsing waves, rain, ships and marine animals (particularly snapping shrimp!) create quite a cacophony. The audio signatures generated by submarine machinery and propellers are distinct, however, and their propagation must be reduced profoundly so a sub can disappear into the background noise. Enemy forces are constantly listening with floating sonobuoys, sonar mines, passive arrays towed by ships and subs, as well as active sonar from those vessels.

The extreme damping and insulation built into a submarine can account for up to half its mass [*see illustrations*]. Once deployed, myriad sensors analyze every peep in the $1-billion boats for sounds from aberrations as minor as a loose bolt. "You can't imagine the level of scrutiny," says Nicholas C. Nicholas, a researcher at Pennsylvania State University and former lecturer at the U.S. Naval War College.

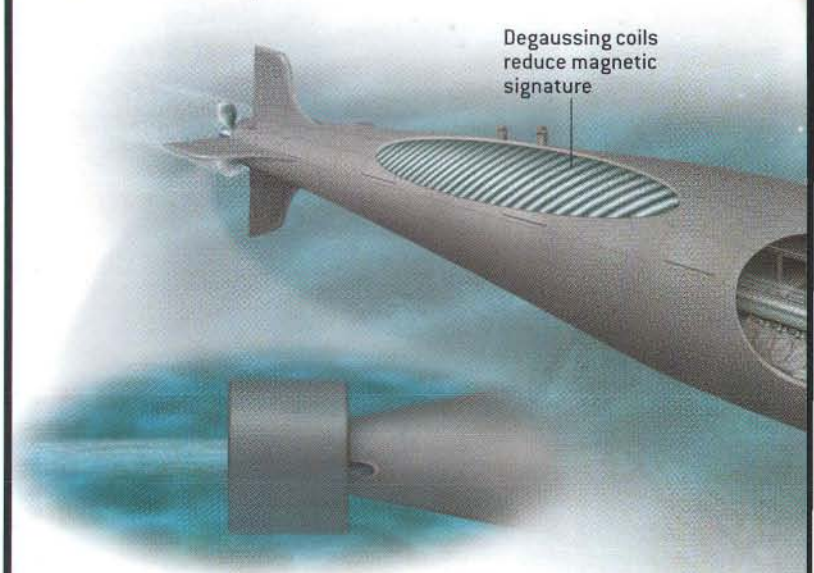
Tactics also come into play. Commanders look to cruise in cold-water eddies or just below boundaries between seawater layers, each of which can help refract sound away from the ocean surface. The crew may run close to the clamorous surface during rainstorms or navigate along polar regions, where the formation, breakup and wave-beating of ice can produce background clatter as loud as 55 to 80 decibels.

Information about silencing subs is highly protected by the military. This column was researched primarily from published reports. (Especially useful sources are *Submarine Technology for the 21st Century*, by Stan Zimmerman, Trafford Publishing, 2000; and *Submarine: A Guided Tour inside a Nuclear Warship*, by Tom Clancy with John Gresham, Berkley Books, 2002.) Techniques are so guarded that human lives may even be subordinate. When the Russian nuclear sub *Kursk* sank in August 2000, the country turned down international rescue help. And sub commanders have orders to destroy their vessel if another nation's seamen are about to board.

—Mark Fischetti

SUBMARINES must quiet acoustical noise from cavitation (*below*), mechanical vibrations (*top* and *bottom right*) and turbulence.

ROTATING PROPELLER creates voids on the low-pressure side that rapidly grow and collapse (cavitate), producing sounds like finger snapping. Special propeller shapes and machining techniques can reduce bubble formation. So can high water pressure, motivating subs to cruise deep.



PUMP JET, or propulsor, replaces the propeller on new subs such as those in the Virginia class. It operates like a turbine, creating less noise, fewer bubbles and more efficient thrust. Cowlings reduce turbulence around the propulsor and other structures.

RAFTS, akin to rubber beds, dampen vibration from heavy equipment. The rafts' enormous mass absorbs vibrations, and lattice structures reduce resonance. Feedback units may actively cancel remaining frequencies.

KENT SNODGRASS *Precision Graphics*

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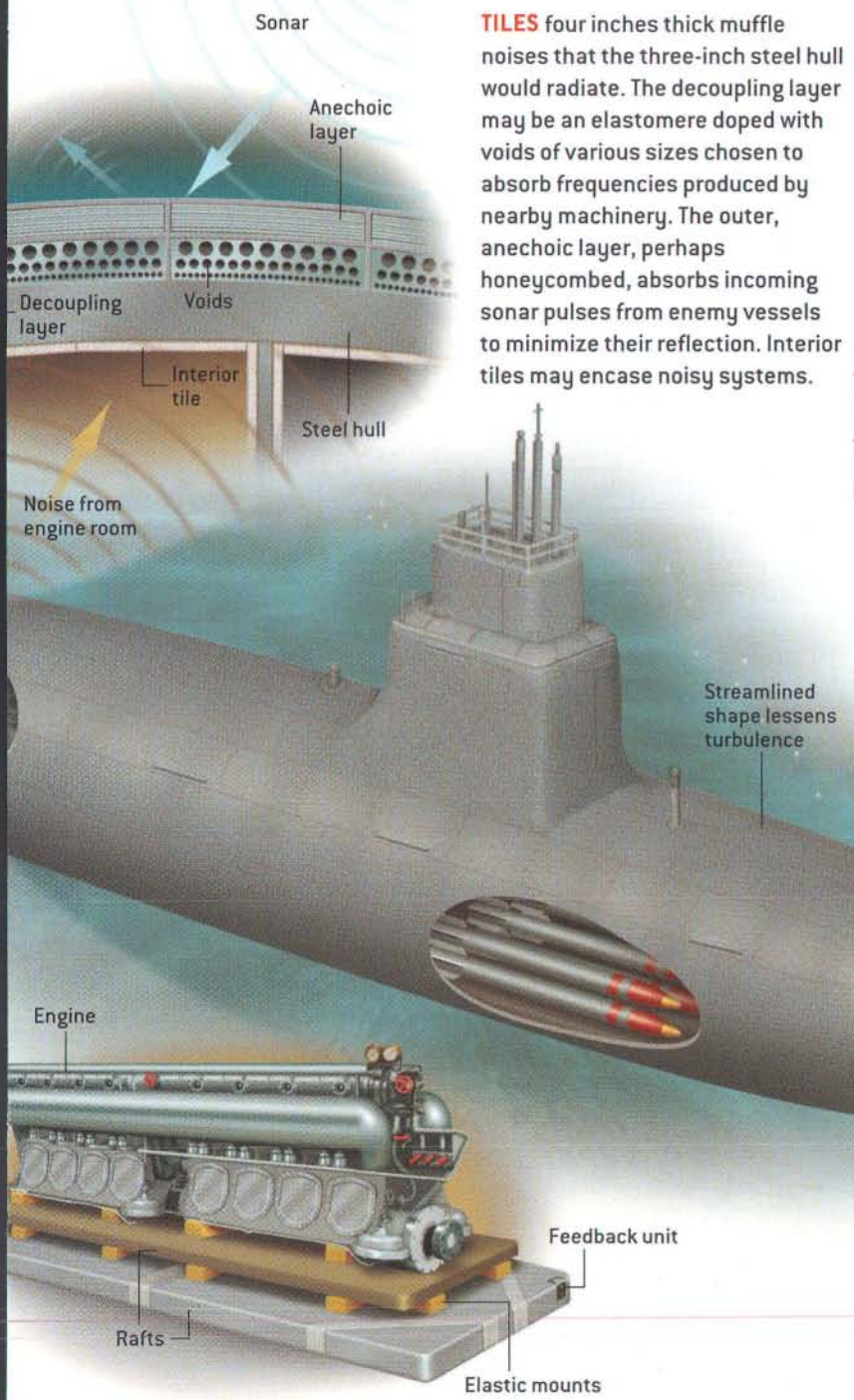
DID YOU KNOW . . .

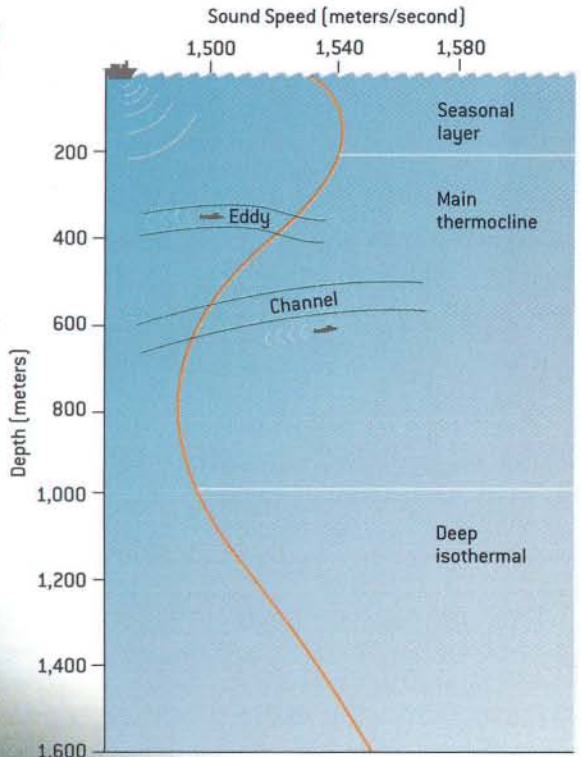
➤ SOUND STEEL: The deeper a sub dives, the better it can avoid detection. But saltwater pressure increases by about 44.5 pounds per square inch (psi) for every 100 feet of depth. Hulls had long been made with "high-yield" nickel-carbon steel alloys that can withstand 80,000 psi (known as HY-80), which corresponds to a crush depth of 1,800 feet. Recent subs, such as the USS *Seawolf*, are built from HY-100 steel, extending the dive limit. The Russian Sierra class, made of titanium, can reportedly reach well beyond 2,400 feet.

➤ SEA MAGNET: Navies have long tinkered with a magnetohydrodynamic propulsion system like that featured in the 1990 movie *The Hunt for Red October*. In accordance with the Lorentz principle (a magnetic field will accelerate a charged particle moving at right angles to it), ionized seawater would be accelerated through a shaft surrounded by powerful magnets, creating propulsion. The system would be incredibly quiet, eliminating the propeller, drive shaft and heavy gears. But energy efficiency is very low. Japan launched a 100-foot prototype sub, but indications are that it performed poorly.

➤ SUPERSMOOTH: It takes weeks of machine milling plus months of hand finishing to make a typical 20-foot-diameter, 41-ton propeller smooth enough to limit cavitation. The U.S. Navy was set to introduce much quieter propellers in 2002, but an Asian company reportedly gave away the technical secrets to Russia, undermining the advance.



TILES four inches thick muffle noises that the three-inch steel hull would radiate. The decoupling layer may be an elastomere doped with voids of various sizes chosen to absorb frequencies produced by nearby machinery. The outer, anechoic layer, perhaps honeycombed, absorbs incoming sonar pulses from enemy vessels to minimize their reflection. Interior tiles may encase noisy systems.



SOUND TRAVELS 1.7 meters per second faster for every 100 meters in depth because of rising water pressure but slows because of dropping temperature. Below about 1,000 meters, ocean water is a steady 36 degrees Fahrenheit. The resulting sound speed profile (*above*) affects refraction and thus where a sonar pulse travels, as well as the calculation for how far away a target object is. The profile varies considerably in the surface layer because of changing weather, solar heating and radiational cooling. To avoid detection, subs may operate in cold-water eddies or just below layers of water with differing temperatures, to scatter sounds along with the "ping" emitted by searching sonars.

Security at Your Fingertips

FINGERPRINT SENSORS CAN GUARD YOUR COMPUTER DATA BY MARK ALPERT

Like many children of the 1960s, I have long entertained James Bond fantasies. While walking to work in midtown Manhattan, I often imagine myself as an agent for the British intelligence service, hunting down Dr. No or Goldfinger or Blofeld as the silhouettes of beautiful women dance languidly in the background. I drink vodka martinis (shaken, not stirred), and I would certainly drive an Aston Martin if I could afford one.

I recently got a chance to act out my spy dreams after I learned about a new class of fingerprint security systems that can work with your PC or laptop. These relatively inexpensive devices can protect your own top-secret electronic files by recording your fingerprint—any finger or thumb will do—on a small sensor attached by a USB line to your computer. Thereafter anyone seeking to open the files must place a finger on the sensor; if the print does not match the recorded data, access is denied. Fingerprint authentication can also provide an extra level of security when you're conducting transactions on the Internet. And the technology can stop hackers from breaking into corporate or government networks, because it's a lot harder to steal a finger than a password.

For years, researchers have been tinkering with identification systems that could recognize a user's voice, face, handwriting, or patterns in the iris and retina. (The field is known as biometrics.) Fingerprint identification is the simplest method because every print has a unique set of clearly defined markers: the coordinates of the minutiae points, the places where the epidermal ridges begin and end. These points are what the police use to match the fingerprints left at a crime scene with those of a suspect [see "No Two Alike," by Mark Fischetti, Working Knowledge; SCIENTIFIC AMERICAN, March 2003].

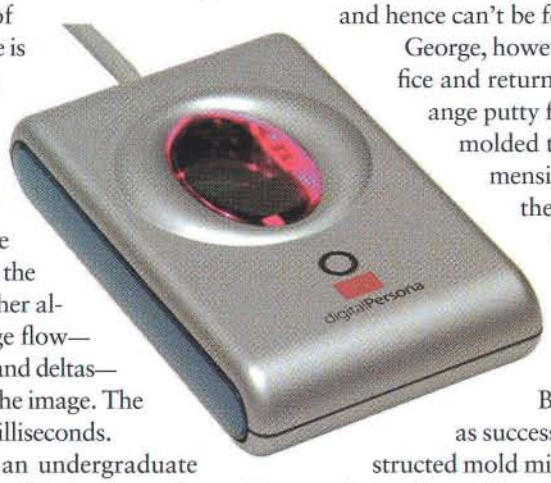
IF DIGITAL IMPERSONATORS are trying to swipe your electronic files or break into your computer network, you may want to install a fingerprint verification system. The software records your fingerprint and allows you to use it as a password for files, networks or online transactions.

In some ways, though, a fingerprint-verification device for PC users must be more fault-tolerant than the systems devised for law-enforcement agencies. Police officers can make sure they get readable prints by carefully rolling a suspect's fingers on a traditional ink card or an electronic scanner. In contrast, most PC users won't be so meticulous; a commercial system must be able to verify their prints even if their fingers are positioned sloppily or speckled with glazed sugar.

The security system developed by DigitalPersona, a firm based in Redwood City, Calif., is designed to recognize even the muddiest fingerprints. The company's U.are.U 4000 sensor is smaller than

a deck of cards and has an oval plastic window on which you place your finger. As your digit nears the window, six LEDs in the device shine light against the inside surface of the plastic. The light is angled in such a way that it is totally reflected if there is nothing but air above the window. But if a substance with a higher index of refraction—such as skin—is pressed against the window, the light will be absorbed at the points of contact, a phenomenon called frustrated total internal reflection. So the reflected light, which is read by a charge-coupled device inside the sensor, bears the pattern of the fingerprint.

The sensor sends the resulting image (encrypted, of course) to your computer's microprocessor. Using a variety of complex algorithms, the DigitalPersona software determines the coordinates of up to 70 minutiae points and packages the data in a 300-byte template. The system compares these templates to match fingerprints; the fingerprint images themselves are erased to prevent any possibility of theft. Because each template also contains data about the angles of the fingerprint ridges, the software is able to make a match even when the orientation of the finger is quite different from its placement when the print was originally recorded. Other algorithms analyze the overall ridge flow—the oddly beautiful loops, whorls and deltas—to decipher any smudgy parts of the image. The entire process takes about 200 milliseconds.



REFLECTED LIGHT reads fingerprint patterns in DigitalPersona's U.are.U 4000 optical sensor.

DigitalPersona grew out of an undergraduate project at the California Institute of Technology. Vance Bjorn, the company's co-founder, developed the key fingerprint-recognition algorithms in the early 1990s with fellow Caltech student Serge Belongie, who is now an assistant professor at the University of California at San Diego. Vance came to my office to show me DigitalPersona's latest products, letting me register one of my fingerprints using a U.are.U 4000 sensor attached to his laptop. I placed my right index finger on the sensor's glowing red window four times in quick succession so the system could create an accurate record. After that point, it recognized my right index finger every time I put it on the sensor and consistently rejected all other fingers and thumbs. The system's design goal is a one-in-50,000 chance of accepting the wrong fingerprint and a one-in-100 chance of rejecting the correct one.

Vance then showed me an even smaller sensor, dubbed the U.are.U Firefly, which is tiny enough to be incorporated into the body of a laptop or PDA. The user runs his or her finger over a half-inch-long transparent rod that rotates like a rolling pin. As the rod turns, LED light bounces off different parts of the fingertip, creating a series of linear images that are stitched together to form the fingerprint. When not needed for fingerprint recognition, the rod can be used to scroll pages up and down the screen.

As I tried out the device, I cried, "This is so cool!" rather loudly. This outburst attracted the attention of my colleague George Musser, who rushed into my office to see what all the fuss was about. George insisted on recording his own fingerprint on Vance's laptop. (The system allows several users to share a computer yet keep their files private.) Then George, who is a preternaturally inquisitive character, tried to figure out a way to fool the system. First he made a copy of his fingerprint using a piece of Scotch tape and ran the imprint over the sensor. But because the device uses several LEDs shining in different directions, it obtains a three-dimensional image of a fingerprint and hence can't be fooled by a two-dimensional copy.

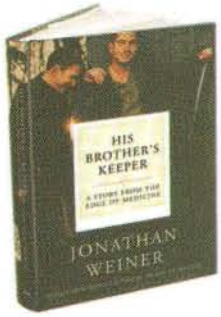
George, however, was undeterred. He retreated to his office and returned a few seconds later with a piece of orange putty from one of the toys on his windowsill. He molded the putty to his finger to create a three-dimensional copy of his fingerprint and ran it over the sensor. Interestingly, James Bond used a similar technique in the 1971 movie *Diamonds Are Forever;* Agent 007 managed to pose as one of Blofeld's henchmen by wearing a set of false fingerprints fashioned by Q, the gadget wizard of the Bond films. George's attempt, alas, was not as successful. Vance conceded that an expertly constructed mold might be able to trick the sensor, but making the mold would require the cooperation of the individual being impersonated.

The growing concerns about identity theft may give a boost to fingerprint-verification technology. If you do your banking or stock trading online, for example, you may feel an extra degree of comfort from knowing that nobody can log on to your account without submitting the proper fingerprint. And the devices are not too hard on the wallet. DigitalPersona's U.are.U Personal system, which is meant for home or office use, retails for less than $100. Other companies offer similar products in the $100 to $200 range: Biolink Technologies International sells the U-Match Mouse, which has an embedded fingerprint reader, and Identix has the BioTouch PC card, an optical reader that can slip into your laptop's card slot.

Beyond the potential advantages of enhanced security, one must also consider the sheer entertainment value of these products. It's fun to seal all your electronic documents from prying eyes, even if your hard drive contains nothing that is classified.

Deploying Science to Desperate Ends

IN THE SEARCH FOR CURES, HOW MUCH IS PERMISSIBLE? BY CLAIRE PANOSIAN DUNAVAN



HIS BROTHER'S KEEPER: A STORY FROM THE EDGE OF MEDICINE
by Jonathan Weiner
HarperCollins, New York, 2004 ($26.95)

"Diseases desperate grown
By desperate appliances are relieved,
Or not all."
—William Shakespeare, *Hamlet*

Not long ago I got an e-mail from Nikki. My high school friend turned lawyer now communicates solely by laptop, propped in an electric wheelchair, twitching her lip to activate her keyboard. She is fed through a stomach tube, and a ventilator breathes for her 24/7. If a fly lands on her face, she is powerless to brush it away. Nikki has amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease. So do 30,000 other Americans, of whom 8,000 die every year.

Stephen Heywood, a six-foot-three carpenter from Boston, was 28 when his motor neurons began to fail. The earliest clue was subtle: he lost his first arm wrestling match in years to his older brother, Jamie. Then he couldn't turn a key in the front door of a house he was restoring. A year later he stumbled and pitched headfirst down a stairway. ALS is nothing if not relentless.

Jonathan Weiner's latest book, *His Brother's Keeper,* is about ALS plus much more. Part biography, part autobiography, it deals with a family's journey into a previously unimaginable realm, Gen Xer Jamie Heywood's desperate desire to use genetic and stem cell technology to turn the tide of Stephen's disease, the author's coming to terms with his own mother's agonizing decline from another form of nerve death, and the current era of "anything is possible now" science. Weiner won the Pulitzer Prize for his 1994 book about evolution, *The Beak of the Finch.* In *His Brother's Keeper,* his prose is just as graceful and steady but far more personal and revealing. Like his subjects, Weiner is also on a journey.

Clearly, a kinship links the author and the Heywood brothers. For one thing, they share eerily similar intellectual roots. Stephen and Jamie's father is a mechanical engineer on the faculty at the Massachusetts Institute of Technology (Jamie also graduated from M.I.T. with a degree from his dad's department). Jerome Weiner, Jonathan's father, is an engineering professor at Brown. In the course of the book, Weiner asks his father about Jamie's extreme makeover from high-tech entrepreneur to guerrilla bioscientist. His father replies by likening genes, DNA and protein to any other system—a pulley, a circuit, an engine. At which point the writer adds drily: if what has broken is nothing but a system made of molecules, engineers try to fix it.

Unfortunately, ALS is not that easily fixed. When Stephen was diagnosed in 1998, the only FDA-approved drug for the disease was a glutamate blocker (glutamate is a chemical that carries signals between the brain and the spinal cord but also damages the nervous system when released in excess). Convinced that repairing the glutamate transporter protein system is a hopeful tactic for ALS sufferers, Jamie and his scientific collaborators Jeffrey Rothstein of Johns Hopkins University and Matt During of Jefferson Medical College plan to insert the corresponding gene in Stephen's cells. Until fate works against them, that is. A teenager with a rare metabolic disease dies after undergoing experimental gene therapy, Jamie's project is tabled, and During proceeds to plan B: injecting millions of stem cells into Stephen's spinal canal.

I longed to hear more from two voices throughout this otherwise fine and

"THE HEYWOODS mean the whole story to me now," writes author Jonathan Weiner, "an allegory from the edge of medicine. A story to make us ask ourselves questions that we have to ask but do not want to ask. How much of life can we engineer? How much is permitted us? What would you do to save your brother's life?"

moving book. Over a 25-year career, Robert Brown, the ALS specialist at Harvard Medical School who diagnosed Stephen, has led thousands of patients where no one wants to go: the edge of a cliff looking straight down. His perspective would have balanced Jamie's frantic race for a magic bullet. The other voice I missed was Stephen's. Not his matter-of-fact statements, which do weave through the narrative, but his inner thoughts. Was this omission dictated by Stephen himself or the author's delicacy, I wondered.

The 1990s—officially deemed "The Decade of the Brain"—did yield remarkable new facts about the human nervous system as well as breakthroughs in ways of reengineering cells. What is both poignant and telling is Jamie's (and possibly Weiner's) notion that science might, as a result, rescue ALS victims on a specific timetable. Medical miracles do not obey timetables, even in an era of quantum scientific leaps.

But there are other miracles in this book and in the lives of ALS patients. In 1999 Jamie Heywood launched a fledgling organization called the ALS Therapy Development Foundation. Today it is well funded and staffed, supporting a number of important research efforts. Stephen Heywood married and had a child, despite the inexorable progress of his disease. And Nikki, my dear friend, continues to engage with life: electronically overseeing her household; cheering husband, family and friends; attending her kids' school and sports events and a biweekly book club. In ALS, the triumph of the human spirit is the greatest miracle. *His Brother's Keeper* may focus on the promise of science, but the mystery of transcendence also speaks from its pages loud and clear.

Claire Panosian Dunavan is professor of medicine and infectious diseases at the David Geffen School of Medicine at U.C.L.A. and a medical writer.

THE EDITORS **RECOMMEND**

MY FAMILY ALBUM: THIRTY YEARS OF PRIMATE PHOTOGRAPHY

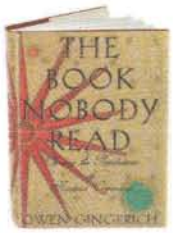
by Frans de Waal. University of California Press, Berkeley, Calif., 2003 ($29.95)

"Human laughter derives from the primate's 'play face.' Not only do the human and ape expressions look alike—with half-open mouth and relaxed muscles around the eyes—the accompanying sounds, too, have much in common. In bonobos, laughter is a hoarse, rhythmic breathy sound heard especially during intense tickling matches. In the ... photo, a juvenile bonobo shows the 'classic' play face with the upper teeth covered." So writes de Waal in this book of exceptional photographs and witty, informative captions. One of the world's foremost primatologists, he is C. H. Candler Professor of Primate Behavior at Emory University and director of the Living Links Center at Yerkes Primate Center in Atlanta.

THE BOOK NOBODY READ: CHASING THE REVOLUTIONS OF NICOLAUS COPERNICUS

by Owen Gingerich. Walker & Company, New York, 2004 ($28)

In a 1959 best-selling history of astronomy, Arthur Koestler called Copernicus's *De revolutionibus* (which set forth the controversial view that the sun rather than the earth is at the center of the universe) "the book that nobody read." Gingerich, then an astrophysicist at Harvard University, happened on a first edition from 1543 richly annotated by a well-known 16th-century astronomer. At least one person had read the book! His fascination with this find turned Gingerich into a full-time historian of science and, to prove Koestler wrong, sent him on a 30-year odyssey to examine every first edition he could track down. This is the story of that quest, in which Gingerich covered hundreds of thousands of miles, uncovered 276 first editions and showed that Koestler was, indeed, wrong. The marginal notes, especially in copies that had belonged to other astronomers, reveal how much Copernicus's thesis was being debated by his contemporaries. Part detective thriller, part vivid historical biography, it's all fun.



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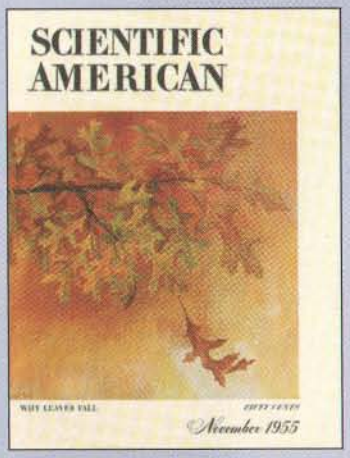
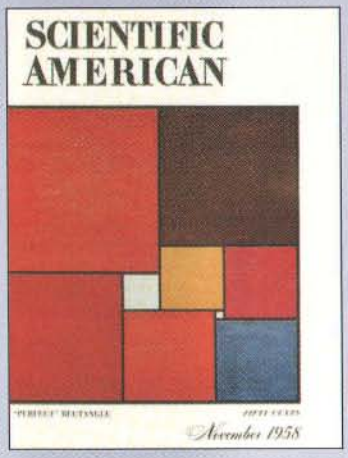
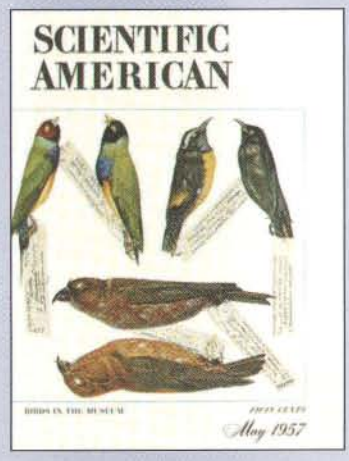
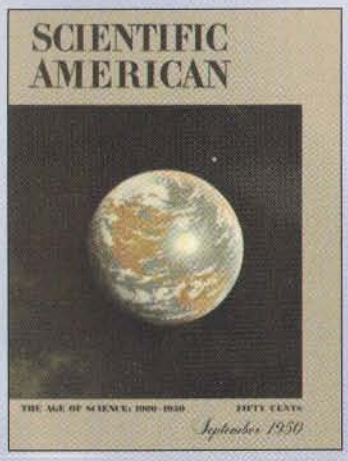
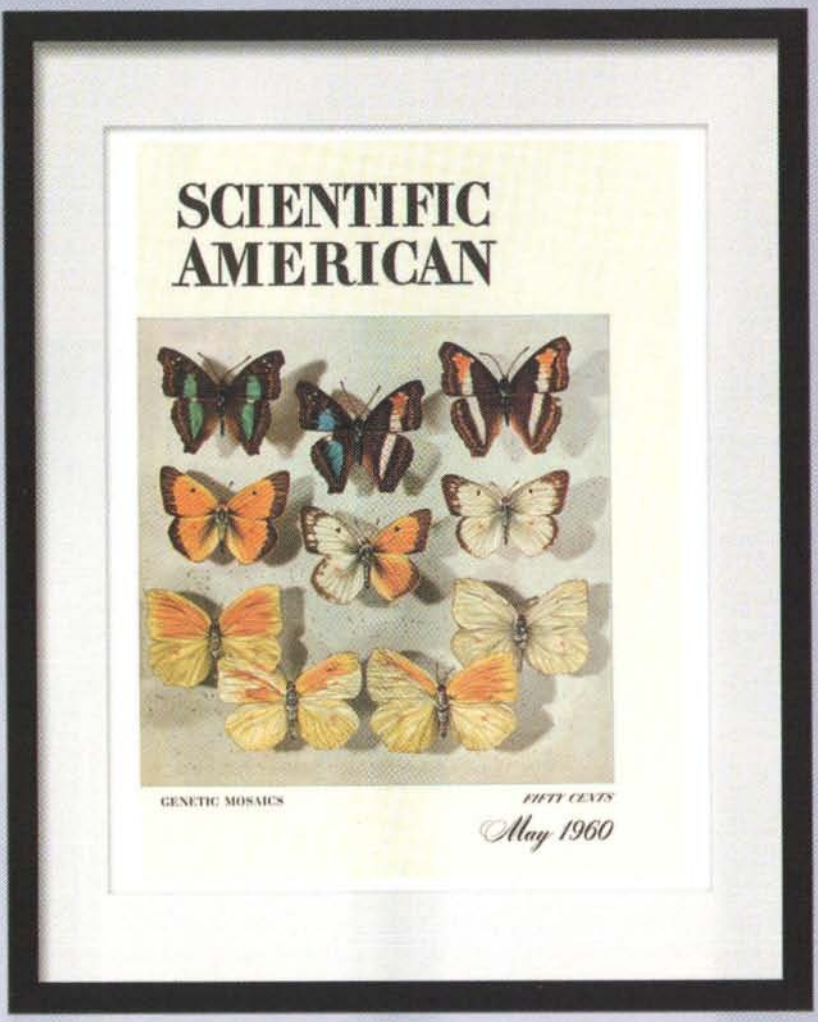
The Art Of Science











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Take This Job and Do It

WHY WE TEND TO WATER DOWN OTHER PEOPLE'S WORKLOADS **BY STEVE MIRSKY**

People often underestimate (or misunderestimate in special, high-level circumstances) the difficulties inherent in other people's jobs. Wake Forest University football coach Chuck Mills once summed up the phenomenon with this description of the average college football fan: "He's the person who sits 40 rows up in the stands and wonders why a 17-year-old kid can't hit another 17-year-old kid with a ball from 40 yards away. Then he goes out to the parking lot and can't find his car."

A new study, however, notes that there may be an actual neurological basis for our assumptions that other people have easier jobs than our own, or what I have found myself thinking of as "presumptive piker syndrome."

Researchers at University College London's Institute of Neurology hired an actor, who was videotaped picking up small black boxes that weighed between 50 and 850 grams—or 1.76 ounces to 1.87 pounds for the metrically challenged, also known as Americans. Twelve test subjects then watched the uplifting performance while themselves raising boxes. One fascinating finding was that when the subjects were themselves lifting a 750-gram box, one of the heavier ones used in the experiment, they judged the box that the actor was hoisting in the movie to be significantly lighter, by 61 grams on average, than it actually was.

The study authors, in the March 23 issue of *Current Biology*, note that the way our brains work may make such a judgment inevitable. When you simply watch someone else do something, they write, "the observer's motor system may simulate the other person's behavior, and this simulation contributes to the observer's understanding of that person's movement, intentions and goals." But if you clog up your motor system by making it actually motor, "it is possible that performing an action will interfere with or bias the processing of observed actions." So if you're working hard on the assembly line, or at least at the plant where they pick up and put down small black boxes all day, the

guy next to you doing the same thing is pretty much guaranteed to look to you like he's slacking off.

Despite a newfound sympathy for the plight of the employed, one can still wonder just what the heck the people with the job of being city councilors in Aliso Viejo, Calif., were thinking in March. They had scheduled a vote on banning foam cups at city events, because the dangerous compound dihydrogen monoxide (DHMO) is used in their manufacture. DHMO is, of course, a clever chemi-calumnious way to say "water." The council members were probably all steamed up by a subtly satiric Web site (www.dhmo.org) that lists some of the dangers associated with DHMO and points out that it is used in the production of Styrofoam. The Web site also includes warnings such as a danger of "death due to accidental inhalation of DHMO, even in small quantities"; "prolonged exposure to solid DHMO causes severe tissue damage"; and DHMO "is a major component of acid rain." That's drowning, frostbite and the rain part, for those keeping score at home.

The Web site also states that "research conducted by award-winning U.S. scientist Nathan Zohner concluded that roughly 86 percent of the population supports a ban on dihydrogen monoxide." In 1997 Zohner was a 14-year-old high school student in Idaho who won a science fair with his survey about DHMO. He cited the potential negatives, as on the Web site, and 43 of the 50 people he asked thought the compound should be banned.

Some Web criticism about the Aliso Viejo ruckus was aimed at environmentalists, who were accused of having engendered a sky-is-falling mentality across our great nation. I just assumed, however, that the ease with which Zohner's subjects and the city council got punked showed the need for better science education. Which might also decrease the misunderestimation of some jobs, such as quarterback or global climate researcher. SA

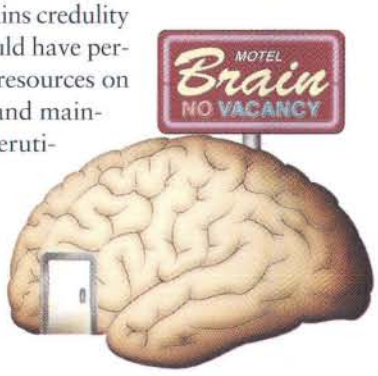
ASK THE EXPERTS

Do we really use only 10 percent of our brains?

Barry L. Beyerstein of the Brain Behavior Laboratory at Simon Fraser University in Vancouver offers this answer:

Perhaps it is unwelcome news, but neuroscience has found no vast, unused cerebral reservoir for us to tap. In addition, a study of self-improvement products by a National Research Council panel found that no "brain booster" is a reliable substitute for practice and hard work when it comes to getting ahead in life.

Why would a neuroscientist immediately doubt that 90 percent of the average brain lies perpetually fallow? First of all, it is obvious that the brain, like all other organs, has been shaped by natural selection. Brain tissue is metabolically expensive to grow and to run, and it strains credulity to think that evolution would have permitted the squandering of resources on a scale necessary to build and maintain such a massively underutilized organ.



Moreover, doubts are fueled by ample evidence from clinical neurology. Losing far less than 90 percent of the brain to an accident or disease has catastrophic consequences. There does not seem to be any area of the brain that can be destroyed by stroke or other trauma without leaving the patient with some kind of functional deficit. Likewise, electrical stimulation of points in the brain during neurosurgery has failed so far to uncover any dormant areas where no perception, emotion or movement can be elicited by applying these tiny currents. (This can be done with conscious patients under local anesthetic because the brain itself has no pain receptors.) With the aid of tools such as EEGs, magnetoencephalographs, PET scans and functional MRIs, researchers have succeeded in localizing a myriad of psychological functions to specific centers and systems in the brain. With nonhuman animals, and occasionally with human patients undergoing neurological treatment, recording probes can even be inserted into the brain itself. Despite this detailed reconnaissance, no quiet areas awaiting new assignments have emerged.

The 10 percent myth has undoubtedly motivated many people to strive for greater creativity and productivity in their lives—hardly a bad thing. The comfort, encouragement and hope that it has engendered help to explain its longevity. But like so many uplifting myths, the truth of the matter seems to be its least important aspect.

How can the weight of Earth be determined?

—A. Thor, San Diego, Calif.

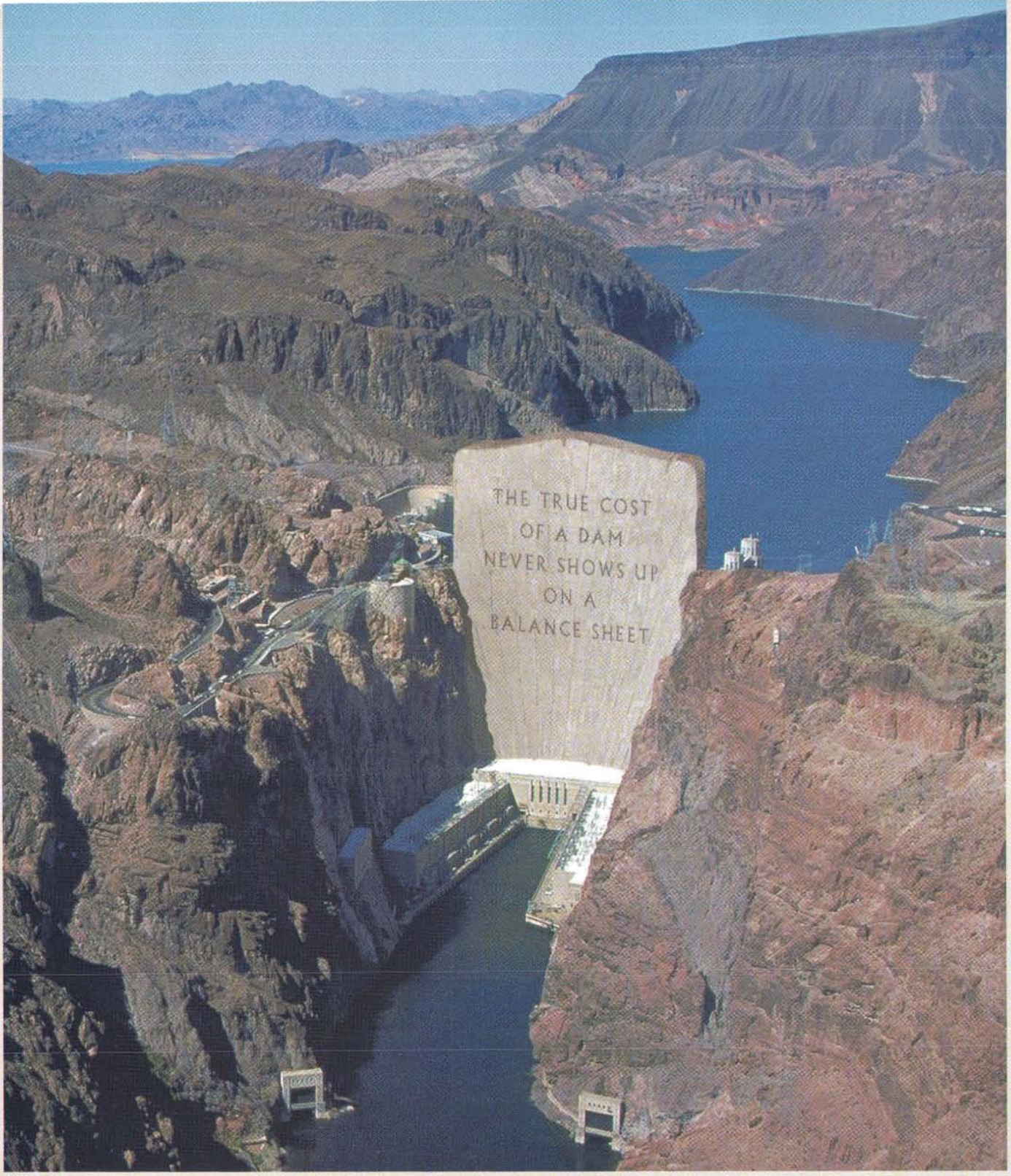
Michael Wysession, associate professor of earth and planetary sciences at Washington University, explains:

I think the reader is really asking about the mass, rather than the weight, of Earth. But we can still solve this problem using a bathroom scale, which you might typically use to weigh something.

As is often the case in physics, fairly complicated things can be described very well with a simple equation. To determine Earth's mass, we can use the formula $g = G \times$ (mass of Earth)/distance to Earth's center^2. The rate at which an object accelerates as a result of the force of gravity, called g, depends on the mass of the object doing the pulling. From many decades of careful experiments we know G, the gravitational constant, 6.67×10^{-11} ($m^3\ kg^{-1}\ s^{-2}$), where m is meters, kg is kilograms and s is seconds. And we know how far a person standing on the surface is from the planet's center (6,371 kilometers).

To solve the problem, you can drop your bathroom scale out the window and count how many seconds it takes to hit the sidewalk. Then measure the distance from the window to the ground, and you can compute the acceleration of the scale. The answer you will get is 9.8 meters per second per second. Knowing this value of g, along with the constant G and the distance to Earth's center, you can then calculate Earth's mass to be 6×10^{24} kilograms. (You also won't be bothered by bad news from your scale anymore.)

For a complete text of these and other answers from scientists in diverse fields, visit www.sciam.com/askexpert



ON PAPER, dams may seem like a good idea. The truth is dams kill a river's ecosystem by cutting off its flow. But that's after the locals have lost their homes. Spare a thought too, for those downstream of the dam where there's less water to irrigate crops and catch fish. Then there are the green-house gas emissions due to vegetation rotting in the reservoir. Not good. But let's talk money. The projected financial cost is rarely accurate. The World Commission on Dams found that, on average, large dams go over budget by 56%. They are high-risk investments. So how can you navigate this moral and economic minefield? By getting hold of WWF's Investor's Guide to Dams. It outlines good dam practice and alternatives for supplying water and energy. That way you can go into any project with your eyes wide open. DAMS. THINK AGAIN.

www.panda.org/dams

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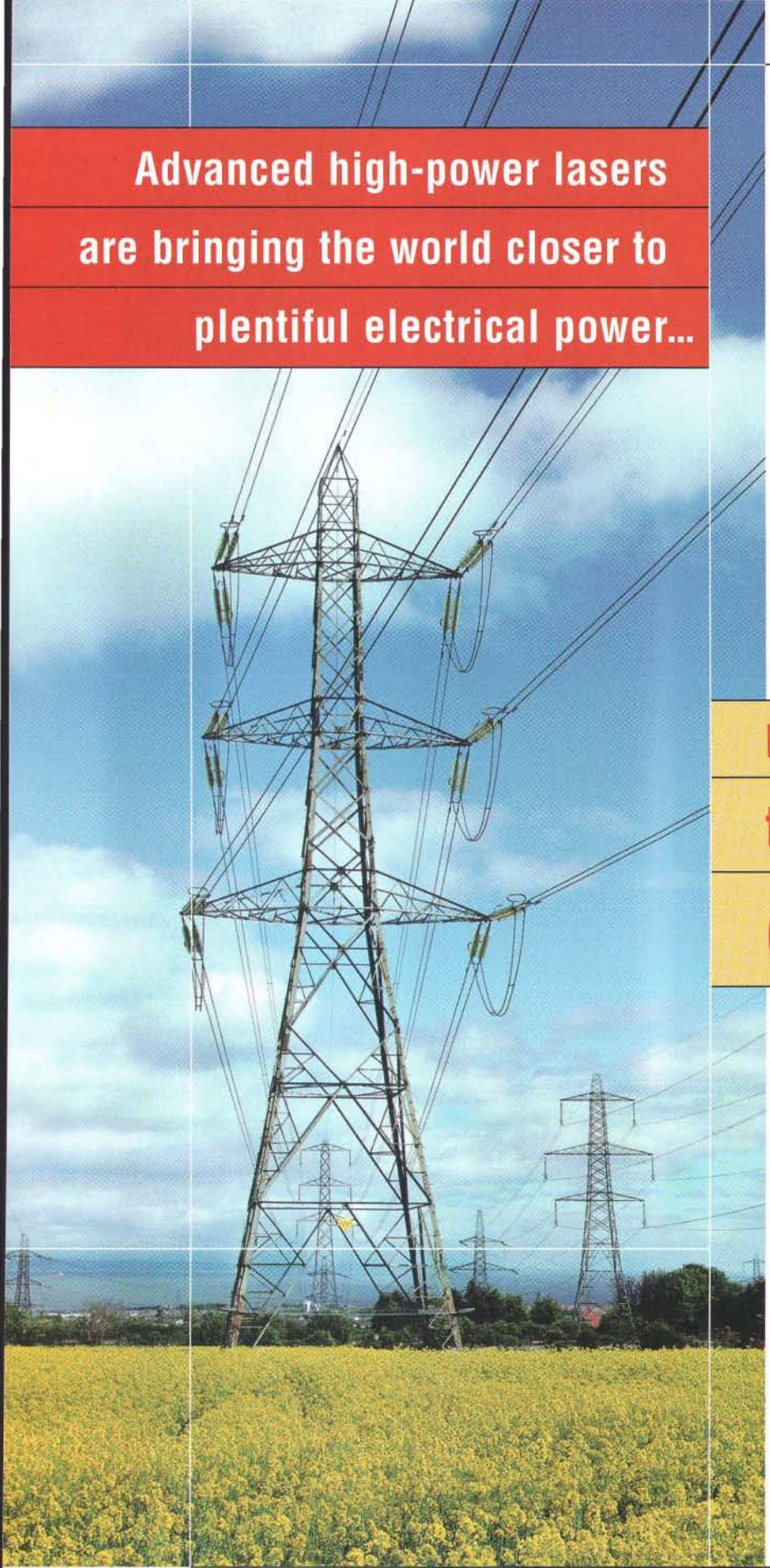

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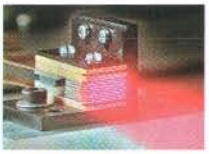

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